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TABLE OF CONTENTS FIRST PAGE

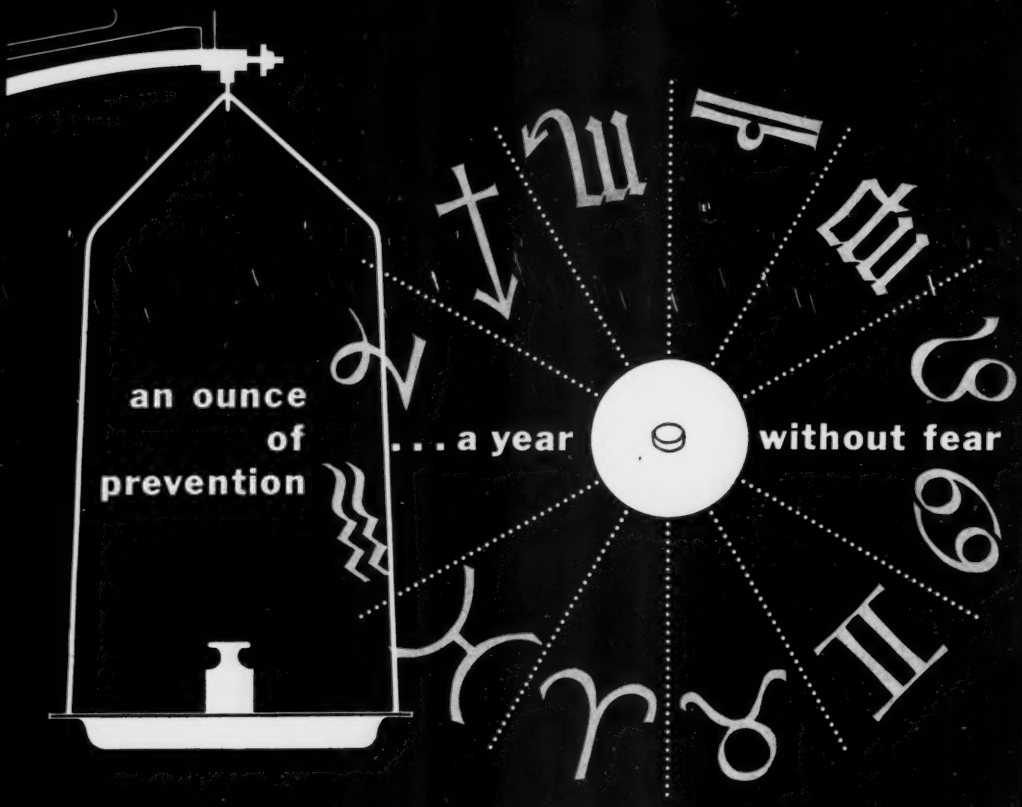

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TABLE OF CONTENTS

EDITORIALS

PAGE

Liver-Function Tests 687

ORIGINAL ARTICLES

Demonstration of Histoplasma and Coccidioides in So-Called Tuberculomas of Lung

Lieutenant Colonel Lorenz E. Zimmerman, Medical Corps, United States Army 690

Effect of Posture on Alveolar Gas Tension in Tuberculosis

William Dock, M.D., Brooklyn 700

Nephrosis and Fat Embolism in Acute Hemorrhagic Pancreatitis

Matthew J. Lynch, M.D., M.R.C.P. (Lond.), with Technical Assistance of Les D. Mellor, F.I.M.L.T., R.T., Sudbury, Ont., Canada 709

Management of Patients with Mitral Stenosis Before, During, and After Mitral Valvuloplasty

George N. Bedell, M.D., Philadelphia; James W. Culbertson, M.D., and Johann L. Ehrenhaft, M.D., Iowa City 718

A Method for Measuring Venous Tone in Digital Veins of Intact Man

G. E. Burch, M.D., New Orleans 724

Sturge-Weber Syndrome (Encephalotrigeminal Angiomatosis)

Geraldine King, M.D., and Gabriel A. Schwarz, M.D., Philadelphia 743

Vasodilatation, Lowered Pain Threshold, and Increased Tissue Vulnerability

Frank N. Bilisoly, M.D.; Helen Goodell, B.S., and Harold G. Wolff, M.D., New York .. 759

Mitral Commissurotomy

F. Henry Ellis Jr., M.D.; John W. Kirklin, M.D.; Robert L. Parker, M.D.; Howard B. Burchell, M.D., and Earl H. Wood, M.D., Rochester, Minn 774

Nutritional Hepatic Injury

Hans Popper, M.D., and Fenton Schaffner, M.D., Chicago 785

TREATMENT IN INTERNAL MEDICINE

Treatment of Sickle Cell Anemia

Byrd S. Leavell, M.D., Charlottesville, Va 801

PROGRESS IN INTERNAL MEDICINE

Survey of the 1953 Hematology Literature (Continued)

Claude-Starr Wright, M.D.; D. Shelton Mabry, M.S.; Richard D. Carr, M.D., and Anna Mae Perry, B.S., Columbus, Ohio 806

CASE REPORTS

Antibiotic Treatment of Bacterial Endocarditis Due to Enterococcus

Burton Armin Waisbren, M.S., M.D., Milwaukee 846

(Continued on Next Page)

CONTENTS—Continued

SCIENTIFIC EXHIBITS

Portal Hypertension PAGE

Donald C. Balfour Jr., M.D.; Telfer B. Reynolds, M.D.; William P. Mikkelsen, M.D.; Arthur C. Pattison, M.D., and Milton R. Hales, M.D., Los Angeles 853

Viremia in Human and Experimental Poliomyelitis

Dorothy M. Horstmann, M.D.; Robert W. McCollum, M.D.; Anne D. Mascola, and John T. Riordan, New Haven, Conn. 859

CORRESPONDENCE

Timidity and Caveats

Vice Admiral J. T. Boone (MC), U. S. N., Rtd. 863

William B. Bean, M.D., Iowa City 863

REGULAR DEPARTMENTS

News and Comment 864

Books 866

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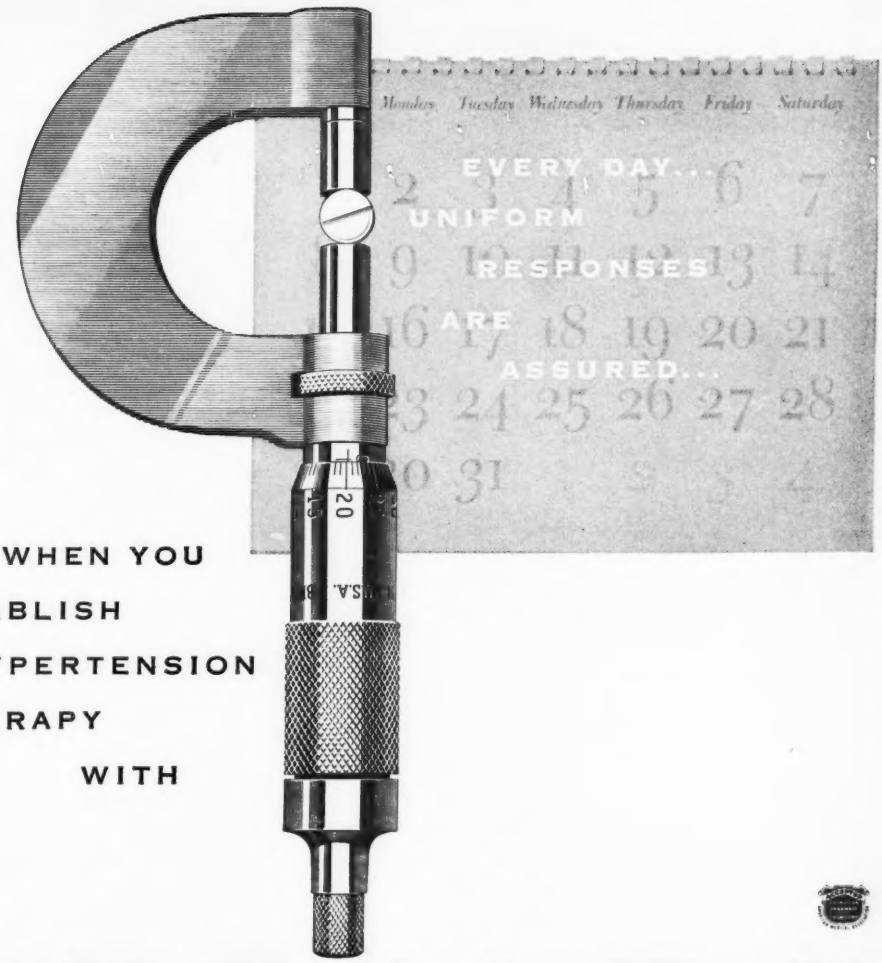

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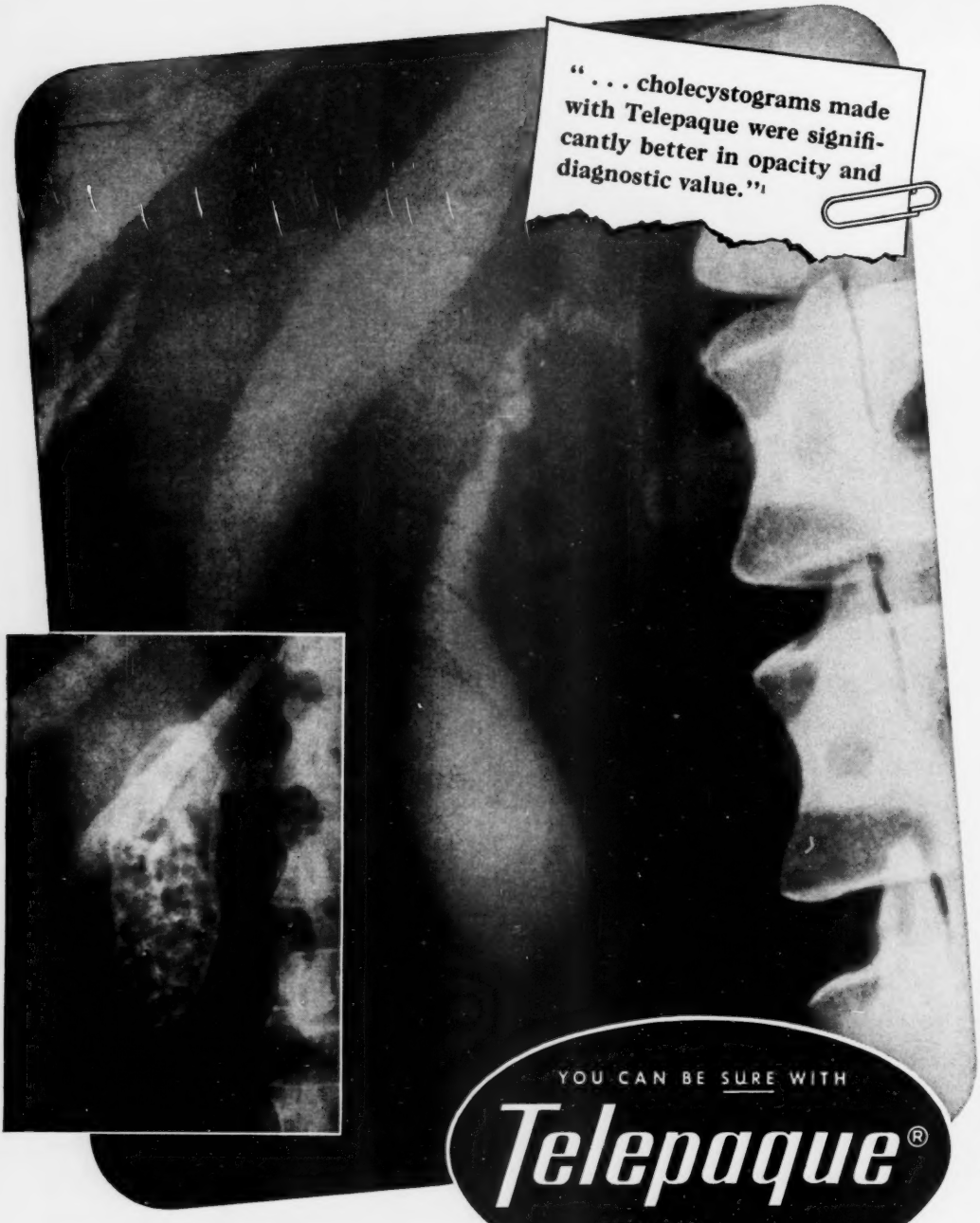

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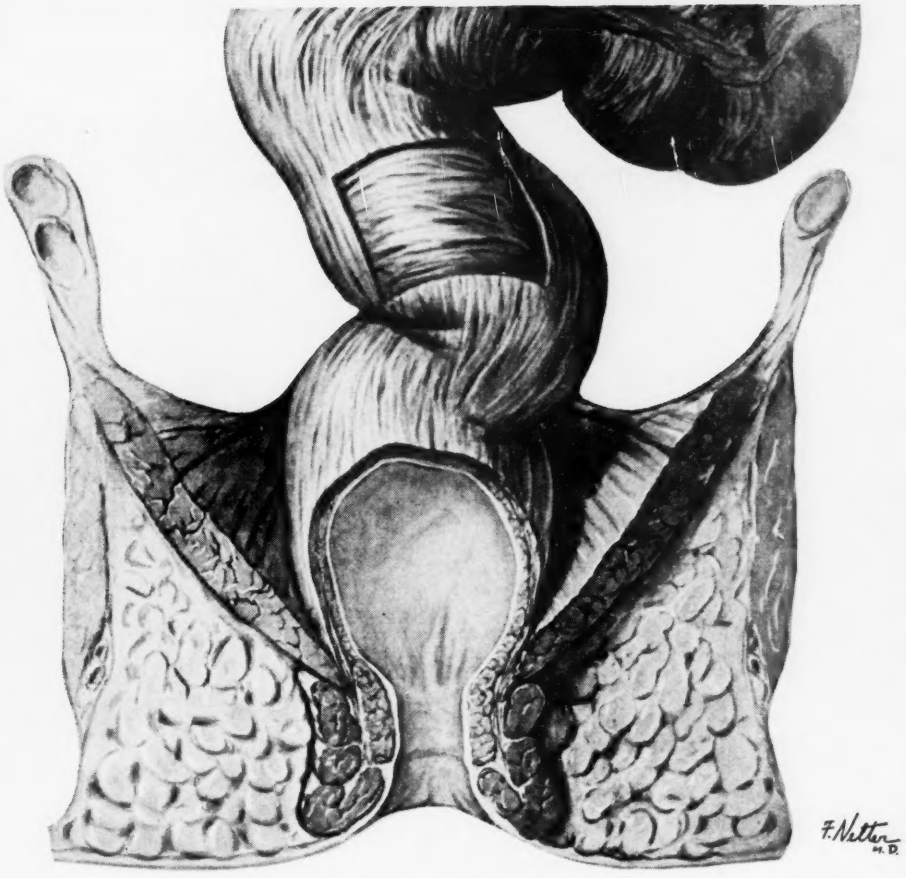

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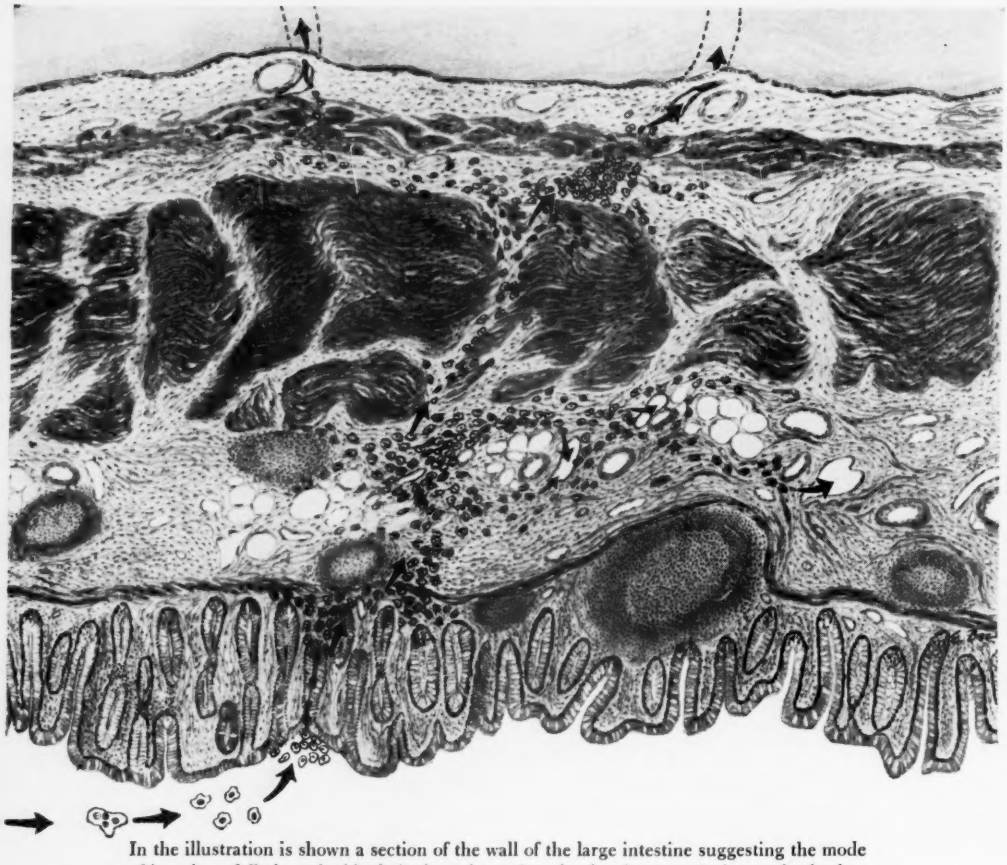

In the illustration is shown a section of the wall of the large intestine suggesting the mode of invasion of *Endamoeba histolytica* into the various levels; the mesenteric venules lead to the liver and escape of some of the parasites may cause an amebic abscess of the liver.

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*Weingarten, M.: Proctology Symposium: Amebiasis: Medical Aspects, Mod. Med. *20*:121 (May 15) 1952.

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Editorials

LIVER-FUNCTION TESTS

NUMEROUS attempts have been made for over half a century to measure the function of the liver by one or another test; these procedures have been proposed for several purposes. First, in cases in which the diagnosis is entirely obscure, it has been hoped that the presence of liver disease might be ruled in or out. Second, in the presence of known liver disease function studies have been used to define, if possible, the degree of damage and the type of lesion. Finally, these procedures seem to have a valuable place in appraising the course of hepatic disturbances—whether downhill or toward recovery. The discovery of the glycogenic activity of the liver, in 1857, by Claude Bernard, stimulated extensive studies of carbohydrate metabolism, and by the late decades of the century alert clinicians were attempting to develop carbohydrate tests for liver function. The general idea was that, if one fed an appropriate dose of a sugar such as dextrose, levulose, or galactose, none would appear in the urine if the liver was normal, whereas glycosuria should occur if there was hepatic disease. A vast amount of work, now mostly obsolete, was done; the carbohydrate liver-function tests were criticized long ago by the writer.[1] Some modifications still maintain a creditable status, however, such as the intravenous glactose test of Althausen.

The first real advance towards a useful procedure was made by Rowntree in 1913. Working with Abel, he had shown that phenolsulfonphthalein was excreted in high concentration by the kidney, but when instead of an SO_2 group four chlorine atoms were added to phenolphthalein, the new compound, tetrachlorphenolphthalein, was almost specifically excreted by the liver. Rowntree and his associates showed that this compound was useful as a measure of functioning liver tissue, since its excretion was much reduced in cirrhosis and in extensive carcinoma.[2] The main objection to the original procedure was that the dye had to be extracted from the stools, a difficult and awkward maneuver. However, the tetracholorphenolphthalein test was the forerunner of the elegant sulfobromophthalein (Bromsulfalein) test so popular and useful today, the principle of which is quite similar.

Through the years almost innumerable tests for liver function have been devised; Lichtman [3] lists no fewer than 55; more are constantly being described. The idea of most of them is of course to test some known physiological activity of the liver, such as the formation of albumin or of prothrombin, the excretion of bilirubin, or the synthesis of hippuric acid. The more tests used, the more precisely it is thought the function of the liver may be appraised, and in some clinics an impressive liver "profile" is constructed by such methods. Now the rationale of most of these tests

From the Department of Medicine, Stanford University School of Medicine.

seems fairly simple. It is instructive, therefore, to study Hanger's recent penetrating analysis of the subject.[4] Hanger points out the great complexity of what is usually thought of by clinicians as a very simple procedure, such as the conjugation of benzoic acid with aminoacetic acid (glycine) to form hippuric acid. Actually it has been shown that this process involves an extremely elaborate reaction which depends on proper availability in the liver of benzoate, specific enzymes of great complexity, high energy phosphate bonds, adequate oxygen and aminoacetic acid, and removal of inhibiting substances from the reacting system. Hanger analyzes certain other types of liver-function test and points out their fundamental complexity and the difficulty of formulating the rationale of their use. It seems, therefore, that in clinical work one is really thrown back on a largely empirical basis. The "test" must be carefully correlated with the type of disturbance which it is supposed to reveal; if it gives useful practical information, well and good. It appears that one should not demand much more than this in everyday work.

What then should be the attitude of the doctor towards the "embarrassment of riches" which is available in the domain of liver-function tests? To do a great many procedures in each case is obviously futile and expensive; it seems better to select a few useful tests and to become thoroughly familiar with them. Some sort of measurement of blood bilirubin is often of great value; an excess may reveal an early latent cirrhosis, the beginning of an acute hepatitis, or the subsidence of hepatitis when serial blood bilirubin measurements reach a peak and then begin to decline. Furthermore, elevation of blood bilirubin over a long time, after acute hepatitis, may indicate latent residual damage and hence give a hint for the continuation of safeguarding therapeutic measures. Sulfobromophthalein retention is an excellent test of the degree of anatomical damage; in patients with cirrhosis, obviously in hepatic insufficiency, very high blood retention of dye is the rule, as it is in cases in which the liver is largely replaced by cancer. The cephalin-flocculation test of Hanger, while not an accurate quantitative measure, is very helpful in differentiating parenchymatous liver disease from obstructive jaundice due to cancer of the pancreas or to stone. Progress towards healing of hepatitis may also be signaled by a lessening of the flocculation. Finally, the level of blood albumin is often low when liver damage exists.

These four tests or some similar group along with careful clinical observation are usually sufficient for general orientation as to the diagnosis of liver disease and for following its course. Other tests or measurements may be desirable for special reasons, such as the prothrombin content of the blood in jaundiced patients when operation is to be done, the alkaline phosphatase in obscure deep icterus, or the zinc- and thymol-turbidity tests when disturbance of blood globulin is suspected. Meanwhile new tests continue to be devised which may or may not add information of value. Quite recently, for example, Pierce, Kimmel, and Burns [5] pointed out that the whole group of Sf 0-400 lipoproteins can be correlated with the thymol-turbidity test and that in hepatitis the return of these lipoproteins to normal during convalescence parallels the decline of the icterus index.

An entirely new facet of liver-function testing was developed by Bradley and his associates [6] when they devised methods of estimating hepatic blood flow by passage of a catheter through the heart into the hepatic veins, which enabled them to measure the clearance of sulfobromophthalein by the Fick principle. There are of course difficulties with such a method, as the authors themselves recognize, but

on the whole useful information has been obtained. By somewhat similar methods Myers [7] was able to estimate not only blood flow but oxygen consumption, and a good many studies along similar lines have subsequently been done.* Although liver catheterization is still definitely a research procedure, it appears that really valid studies of hepatic function can be obtained, and the test of the future may be developed by some such method.

Needle biopsy of the liver is of course often an invaluable supplement to purely physiological appraisal.

ARTHUR L. BLOOMFIELD, M.D.

* See, for example, Bradley and others.[8]

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DEMONSTRATION OF HISTOPLASMA AND COCCIDIOIDES IN SO-CALLED TUBERCULOMAS OF LUNG

Preliminary Report on Thirty-Five Cases

LIEUTENANT COLONEL LORENZ E. ZIMMERMAN
MEDICAL CORPS, UNITED STATES ARMY

DISCRETE encapsulated solitary pulmonary granulomas of the type exemplified by Figures 1 and 2 have long been considered due to infection by the tubercle bacillus and, in fact, are commonly labeled "tuberculoma" by clinician, radiologist, and pathologist alike. Such lesions are usually discovered incidentally on "routine" roentgenographic examinations of asymptomatic subjects. When there is calcification, with or without a distinctly laminated pattern, the roentgenologist is often able to predict the inflammatory character of the lesions.[1] Other lesions, presumably of shorter duration, may present a perfectly homogeneous opacity in the x-ray film and may therefore be confused with a primary or metastatic neoplasm (Fig.3). The proportion of these "coin lesions" which prove to be granulomas (so-called tuberculomas) after surgical removal has been reported as varying from 25% (Davis and Klepser[2]) to 87% (Mahon and Forsee[3]) depending on the nature of the hospital population and individual criteria for inclusion of cases.* In most series so far reported, a "coin lesion" that proved to be a granuloma was assumed to be tuberculous. Noteworthy exceptions are those from the Mayo Clinic.† As Hodgson and McDonald have stated,

> We believe that no granuloma in the lung should be regarded as tuberculous when bacteriologic proof is lacking, and we feel that the word "tuberculoma" should be reserved for those granulomas proved bacteriologically to be due to the tubercle bacillus.[1]

It has been recognized for several years that the fungus Coccidioides immitis may produce a discrete encapsulated peripheral granuloma indistinguishable from the "tuberculoma" by roentgenologic examination or pathologic studies unless the specific agent can be demonstrated within the lesion.‡ Recently, Puckett has shown that organisms morphologically identical with Histoplasma capsulatum may be found in a significant number of these granulomas.§ Before Puckett's demonstration, histoplasmosis had been implicated as a frequent cause of benign pulmonary

Senior Pathologist, Armed Forces Institute of Pathology; Associate in Pathology, George Washington University School of Medicine.

Read before the Section on Pathology and Physiology at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 23, 1954.

* References 1-6.

† References 1 and 5.

‡ References 7-11.

§ References 12 and 13.

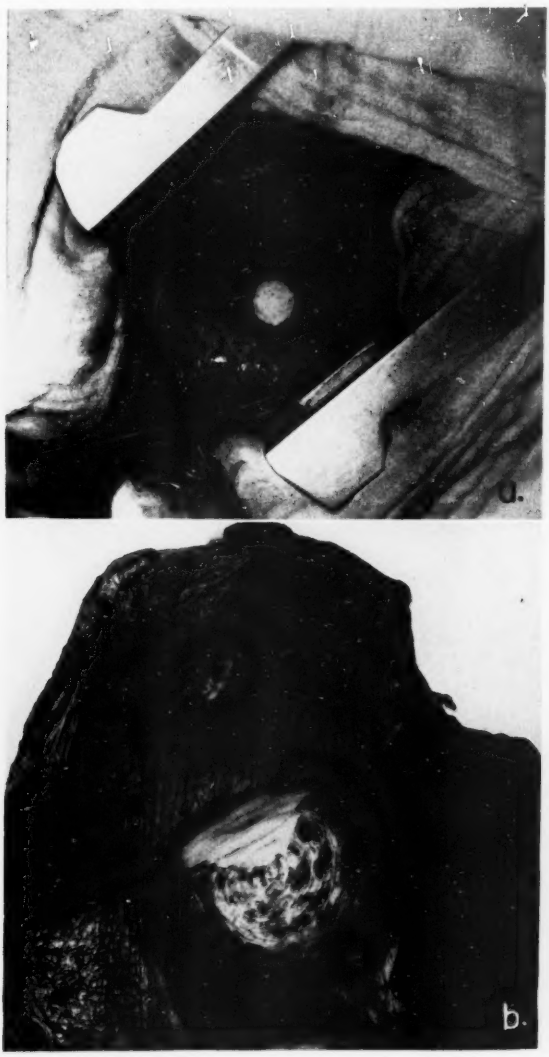

Fig. 1 (AFIP Acc. 194007).—A typical example of the so-called tuberculoma which contained organisms identified as Histoplasma. (*a*) View of pleural surface of lung near apex of right lower lobe as seen at thoracotomy. The characteristic subpleural location and dense hyaline pleural cap are demonstrated. (*b*) Apical portion of the resected lobe, containing the granuloma, which has been bisected. The cut surface reveals a striking degree of lamination except where a conical mass of hyaline extends into the lesion from the pleural surface.

calcification in inhabitants of states bordering the Mississippi River and its tributaries.[14] That Histoplasma may cause chronic pulmonary disease with or without cavitation is also becoming more generally recognized.[15]

The newer techniques for the histopathologic demonstration of fungi || have greatly stimulated the pathologist's interest in medical mycology.[14] Organisms which are invisible in the ordinary hematoxylin-and-eosin-stained slides may be revealed in great profusion by fungus stains. The "tuberculoma" is one lesion in which differential histopathologic stains are even more valuable than culture studies. Cultures (for Mycobacterium tuberculosis and/or fungi) are negative in more than three-fourths of the cases, presumably because the infections are "burned out."¶ The new histologic techniques for the demonstration of fungi are now used rou-

Fig. 2 (AFIP Acc. 314625).—Another example of a "tuberculoma" which contained organisms identified as Histoplasma. (Roentgenogram of this lesion, which was resected from the left lower lobe, is seen in Figure 3*b*). Arrows point to the hyalinized pleural surface of the bisected specimen. The characteristic features of sharp circumscription, abrupt transition from essentially normal lung to granuloma, and lamination about a central necrotic focus are evident.

tinely in the study of all lesions received at the Armed Forces Institute of Pathology as "tuberculoma of lung" or "granuloma of lung, probably tuberculous." Results have confirmed Puckett's # observations, in that Histoplasma has been identified as the causative organism of many of the lesions.

In an effort to ascertain the relative frequency with which acid-fast bacilli, Coccidioides, and Histoplasma may be demonstrated in these lesions, a pilot study of 35 cases was undertaken. In each of the cases selected for this study, the contributing pathologist had made a diagnosis of tuberculosis or probable tuberculosis. Another requirement was that the lesion present the

|| References 16-19.

¶ References 1, 3, 6, 12, and 13.

References 12 and 13.

structural characteristics of "tuberculomas" as outlined by Mahon and Forsee [8] and Black and Ackerman.[20] The macroscopic and microscopic characteristics which distinguish the so-called tuberculoma from pulmonary granulomas of other types have been reviewed elsewhere.[21] Sections of all lesions were stained (Ziehl-Neelsen method) for acid-fast bacilli * and for fungi, the periodic-acid Schiff reaction [17] and the Gridley technique [19] being used. In many instances

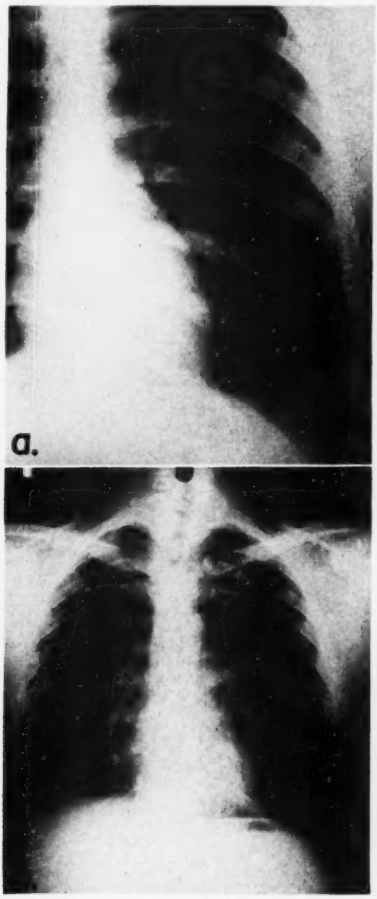

Fig. 3.—(*a*) (AFIP Acc. 204744) Roentgenogram of "coin lesion" near left costophrenic angle (arrow). Calcification is noted in the central portion of the lesion. (Photomicrographs of this granuloma, which proved to be due to Histoplasma, are shown in Figure 5.) (*b*) (AFIP Acc. 314625) Roentgenogram of "tuberculoma" shown in Figure 2. The roentgenographic appearance of the lesion was unchanged during the two years before it was removed.

cultural studies of the granulomas had been undertaken by the contributing pathologists, but the results were uniformly negative. Had the culture been positive and the specific etiologic diagnosis established, the case would have been rejected.

* References 22 and 23.

Results to date are as follows: Acid-fast bacilli were found in 6 cases (Fig. 4); Histoplasma, in 19 (Figs. 5 and 6), and Coccidioides, in 3 (Fig. 7). There remain seven cases in which no organisms have yet been demonstrated. Further studies are in progress on this group.

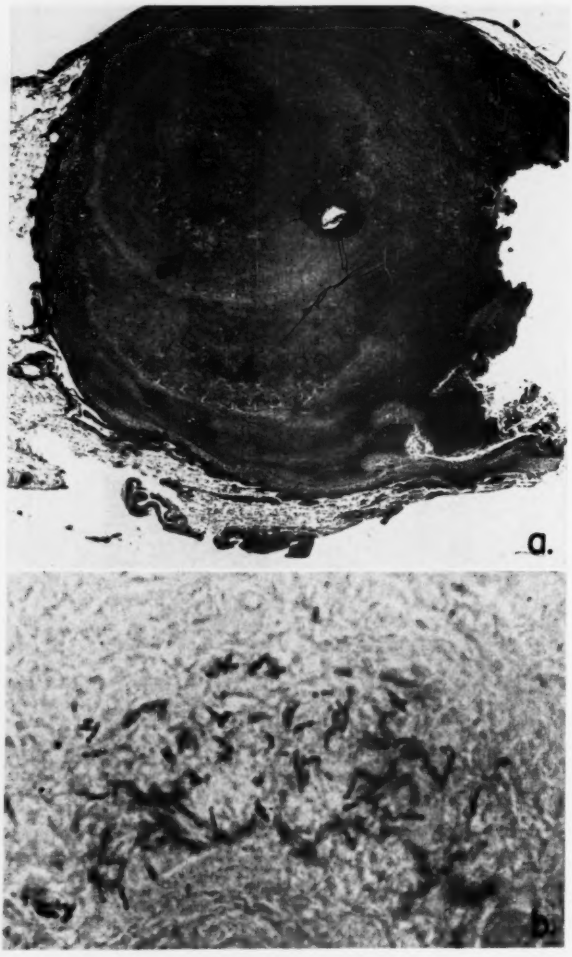

Fig. 4 (AFIP Acc. 234977).—One of the six granulomas in which acid-fast bacilli were demonstrated. (*a*) Subpleural lesion from left upper lobe showing lamination about an eccentric focus of necrosis (arrows) in which the acid-fast bacilli were found. Hematoxylin and eosin; × 7. (*b*) Tubercle bacilli from necrotic area demonstrated by arrows in 4*a*. Acid-fast stain; × 1,460 (oil immersion).

These quantitative data support the impression among the pathologists at the Armed Forces Institute of Pathology who have reviewed cases of this type submitted during the past two years that Histoplasma is the most frequent cause of the granuloma commonly labeled "tuberculoma of the lung." The actual incidence

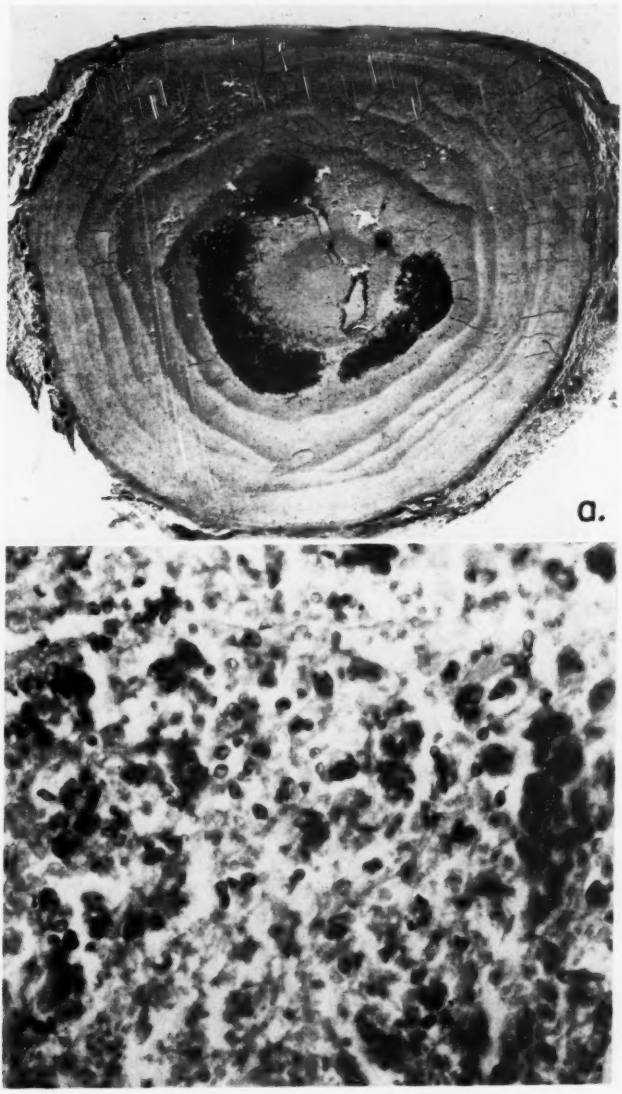

Fig. 5 (AFIP Acc. 204744).—One of the 18 so-called tuberculomas in which Histoplasma organisms were identified. (Roentgenogram of this patient's chest is seen in Figure 3*a*.) (*a*) Subpleural granuloma resected from left lower lobe. Sharp circumscription, abrupt transition from normal lung to lesion, minimal zone of inflammation at periphery, and lamination about a central necrotic focus are characteristic features of this particular type of granuloma, regardless of etiologic agent. A zone of calcification partially surrounds the central necrotic focus in which the organisms demonstrated in 5*b* were found. Hematoxylin and eosin; × 6. (*b*) Organisms identified as Histoplasma are stained pink by the Gridley stain for fungi, in sharp contrast to the pale yellow counterstaining of the necrotic debris in which the organisms are found; × 580 (oil immersion).

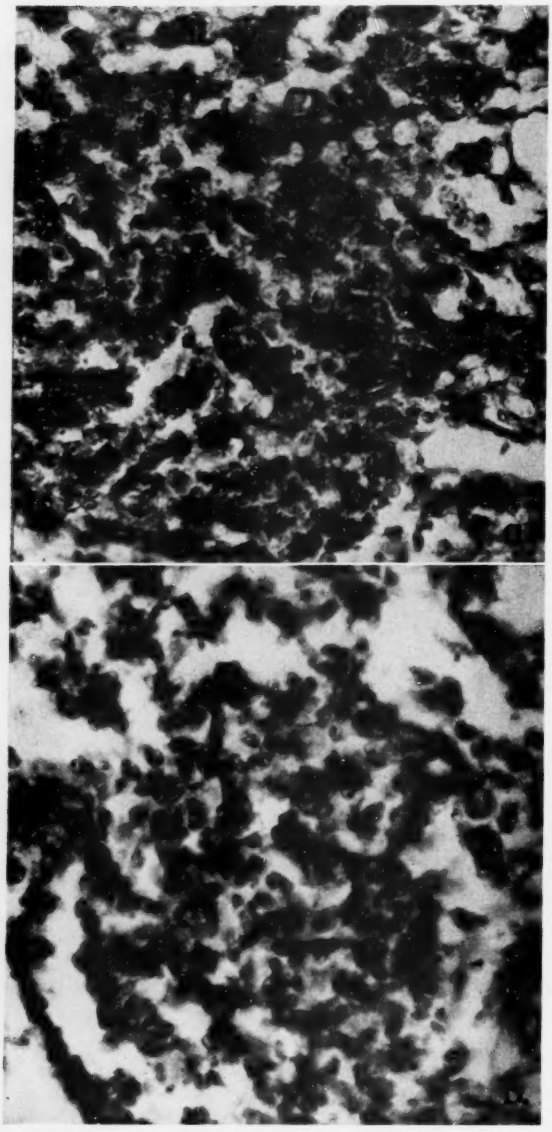

Fig. 6 (AFIP Acc. 125937).—Organisms identified as Histoplasma, stained by the periodic acid-Schiff reaction, from another of the so-called tuberculomas in this series. With this staining technique the organisms have a minute pink central body, which is not demonstrated by the Gridley stain. (*a*) × 650 (oil immersion); (*b*) × 775 (oil immersion).

will vary in different parts of the country, but the present series, based on cases contributed from hospitals all over this country and derived principally from a population of patients who had traveled widely, would constitute a representative sample of what might be found in the United States.

In the search for organisms, be they fungi or acid-fast bacilli, the best hunting grounds are the more or less centrally placed necrotic areas (Figs. 2, 4, 5, and 7).

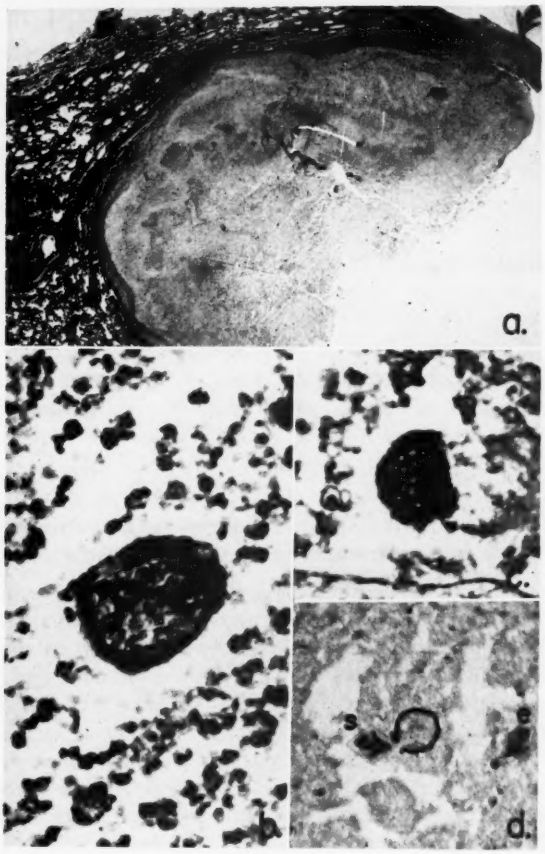

Fig. 7 (AFIP Acc. 182987).—One of the three granulomas which contained Coccidioides. (*a*) Subpleural location (arrow indicates pleural cap), sharp circumscription, abrupt change from normal adjacent lung, and minimal zone of inflammatory reaction about periphery are characteristic features. The central necrotic zone is larger and the laminated pattern less striking than in other lesions illustrated. (*b*) A partially necrotic endosporulating sporangium, as seen in hematoxylin-and-eosin-stained section; × 480. (*c*) Endospores are better demonstrated by special stains. Periodic acid-Schiff; × 500. (*d*) Endospores (Arrow *e*) have been liberated from ruptured sporangium (Arrow *s*). Gridley fungus stain; × 200.

Experience has shown it to be fruitless to search for these organisms in the laminated peripheral fibrosis. Spherules and sporangia of Coccidioides may be found in the hematoxylin-and-eosin-stained section (Fig. 7*b*), but demonstration of acid-fast

bacilli or Histoplasma in this type of lesion demands appropriate staining techniques.† Careful oil-immersion microscopy of multiple sections through the central necrotic area is necessary in order to demonstrate organisms in some lesions. Only occasionally will the acid-fast bacilli or Histoplasma be present in such profusion as is illustrated in Figures 4 to 6. Recognition of Histoplasma in these granulomas is not difficult once the examiner has become familiar with the appearance of the fungus in this situation. However, as Puckett has pointed out,[12] the fungus shows a greater variation in staining intensity, presumably because it is no longer viable, than do the organisms seen in lesions of fatal disseminated infections. Puckett also has illustrated some of the artifacts which may mislead the inexperienced.[12]

In the present study two-thirds of the cases in which the etiologic agent was demonstrated in tissue sections proved to be due to Histoplasma. This would seem to offer an explanation for the high incidence of negative tuberculin skin tests (30%) reported by Mahon and Foree[3] in their series of so-called tuberculomas. These authors apparently had little faith in the reliability of the tuberculin skin test, for they stated: "Histoplasmin and coccidioidin skin tests may be equally positive. The coccidioidin skin test may be positive and the tuberculin negative, yet the lesion proves to be tuberculosis. In other words, skin tests are as often confusing as they are helpful." Their faith in the tuberculous nature of these lesions is difficult to comprehend in view of their admission (in a section of their paper devoted to differential diagnosis) that the nodular lesions of coccidioidomycosis may be differentiated only by demonstration of the fungus. Apparently they required the fungus to make the diagnosis of coccidioidomycosis but were less exacting in the case of tuberculosis. That skin testing is not so unreliable is demonstrated by the series of pulmonary granulomas due to Histoplasma reported by Forsee, Puckett, and Hagman.[13] Only 1 of their 30 patients did not have a positive histoplasmin skin test, while 9 failed to react to first and second strengths of tuberculin.

Determination of the etiology of these surgically resected pulmonary granulomas is not without therapeutic and prognostic implications. The rationale of treating the patient as if he had tuberculosis, which is part of the routine postoperative management of such cases in many institutions, must now be questioned. Regarding prognosis, it is well established that patients with discrete granulomas or cavities due to C. immitis, whether resected or not, may virtually be assured that dissemination will not occur.‡ Comparable follow-up data are not available for patients with granulomas containing Histoplasma, but our knowledge to date would seem to indicate that, as in the case of focalized coccidioidal granulomas, the prognosis is excellent.

SUMMARY

A series of 35 surgically resected discrete pulmonary granulomas presenting typical macroscopic and microscopic features of the so-called tuberculoma was subjected to an intensive search for acid-fast bacteria and fungi. Tubercle bacilli were found in Ziehl-Neelsen-stained sections of six lesions. Special stains for fungi demonstrated Coccidioides in 3 and Histoplasma in 19 cases. There remained seven granulomas in which no organisms could be found.

† References 16-19.

‡ References 24-26.

Drs. C. H. Binford, S. H. Rosen, and L. F. Belter and Dr. C. W. Emmons, National Microbiological Institute, National Institutes of Health, and Special Consultant in Mycology, Armed Forces Institute of Pathology, assisted in this study.

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EFFECT OF POSTURE ON ALVEOLAR GAS TENSION IN TUBERCULOSIS

Explanation for Favored Sites of Chronic Pulmonary Lesions

WILLIAM DOCK, M.D.
BROOKLYN

VALSALVA seems to have been one of the first to point out that progressive lesions of tuberculosis often are confined to the upper lobes,* and Morgagni noted that they favor the upper part of the upper lobes.† Laennec repeatedly emphasized that the disease attacks the apex, and he noted that the initial cavity is found most often on the right side.‡ These facts have been confirmed by innumerable pathologists and radiologists, but in 1951, two and a half centuries after Valsalva's observations, Rich concluded that "it is certainly not possible at present to explain satisfactorily the apical localization of the disease." [3]

In the last three years evidence from several sources has greatly strengthened one of the theories of apical localization. This hypothesis, restated in 1946, after a 50-year eclipse, noted that the pulmonary arterial pressure, then being measured in Cournand's laboratory,[4] was too low in comparison with the force of gravity to maintain flow in the upper third of the lungs when adults were sitting or standing.[5] The resulting change in gas tension in the affected zones was believed to favor growth of tubercle bacilli, but more weight was placed on reduction of lymph-flow and cessation of the dilution of toxins by plasma filtrate as results of the diminished blood flow. The value of bed rest in managing tuberculosis was ascribed to restoration of normal flow in the cephalad part of the lungs.[5]

This theory was first expounded, in 1887, by Johannes Orth,[6] who noted that the weight of the column of blood would cause apical anemia, thus reducing lymph formation. Orth also emphasized the high incidence of pulmonary tuberculosis in patients with pulmonic stenosis. Though Volland, Jacoby, and others espoused this theory in the following decade, it then fell into neglect. Medlar, as a result of his studies of preferential sites in cattle and rabbits,§ recognized that the gravitational field affected resistance to chronic tuberculosis. In these species, when disease is indolent its progress is most evident in the juxtaphrenic region, near the dorsal surface of the lungs. In rabbits, reversal could be affected by keeping the animals' heads and shoulders up by a special harness suspended from a wire. This posture,

From the State University of New York College of Medicine at New York City.

* Hic autem Valsalva animadvertit, ulcus et lesionem in superiore fuisse pulmonum parte (Morgagni [1]).

† Lobus superior, et superiore quidem parte, ulcus intus, nec parvum, habebat (Morgagni [1]).

‡ Les tubercles se développent presque toujours primitivement aux sommets des lobes supérieurs et surtout du droit, et c'est particulièrement dans le dernier que se rencontrent le plus fréquement de vastes excavations tuberculeuses (Laennec [2]).

§ References 7 and 8.

for 11 hours a day, led to localization at the apices, as in man.[8] Thus, in rabbits, as in men, less than half of each day in the erect posture suffices to lower apical resistance.

Paul White summarized published data on the incidence of apical tuberculosis in heart disease, noting high rates in pulmonic stenosis, where arterial pressure in the lung is low, and a low incidence in mitral stenosis, where the pressure is high.[9] He pointed out that pulmonic engorgement retarded, while pulmonic ischemia favored, the development of chronic pulmonary tuberculosis. This circumstantial evidence provided the only basis for the gravitational theory up to 1950. Since then, experiments by Scott, Hanlon, and Olson || have shown that the changes in gas tension created by altered pulmonary flow are of paramount importance in favoring growth of tubercle bacilli and have indicated that changes in lymph flow are unimportant. Others have proved that postural changes alter apical and even lateral gas tension in man.¶ The work on species variation in localization has been extended to the bat, which sleeps hanging head down and has its largest tubercles adjacent to the diaphragm, and to the ferret, with largest lesions scattered along the dorsal subpleural zone.[16] With these data, it is now possible to present a coherent explanation for the favored sites of tuberculosis.

Scott performed three types of operations on monkeys prior to their intravenous inoculation with tubercle bacilli.# One was a sham operation—exposing and severing a pulmonary artery, which was then reunited. This temporarily severed the periarterial lymphatics and caused some trauma but left the blood flow unchanged. Animals thus prepared developed identical lesions in the lobes subjected to operation and in the unoperated lobes. In other groups of monkeys a pulmonary or a lobar artery was either ligated or anastomosed to the innominate or brachial artery after proximal ligation. In either case, no pulmonary arterial blood reached the lobe, and the initial seeding of tubercle bacilli was certainly less than in unoperated lobes, which the intravenous injection reached directly instead of having to go first through the lungs and left side of the heart. Yet, following either of these operations which reduced the number of bacilli reaching the lung affected, the tubercles in the affected lobe were much larger and contained far more bacilli than the miliary lesions in the other lobes. Often there were confluent nodular lesions, rather than miliary tubercles, in the lobes with altered blood supply.

After an anastomosis between a systemic and a pulmonary artery the blood and lymph flow are probably greater than normal, because the systemic arterial pressure is higher. But tubercles evolve more swiftly in a lobe thus perfused than in a lobe to which the pulmonary artery has been ligated, causing a great reduction in blood flow. The anastomosis experiments prove that ample volume and high pressure of arterialized blood entering a lung have no retarding effect on tubercles as long as none of the unsaturated blood returned to the heart by the systemic veins reaches the alveoli. Since the anastomosis provides far more blood than could possibly come from the normal bronchial artery-pulmonary connections, there remains no support for the idea that defense of the basal part of the lung depends largely on abundant inflow of phagocytes and antibodies and on the dilution of toxins by the pulmonary

|| References 10-12.

¶ References 13-15.

References 10-12.

arterial flow. Scott's experiments force one to accept the conclusion that only levels of gas tension are involved in protecting the base or in favoring tuberculosis at the apex. One must also conclude that small changes in gas tension, within the physiologic range, are far more important to the tubercle bacilli in the tissues than could have been predicted from studies of mycobacteria in vitro or from the effects of low O_2 tension on the experimental disease in guinea pigs.

No one has reported the effects on the growth or metabolism of Mycobacterium tuberculosis of changing the gas tension over cultures from levels equivalent to those in expired air (O_2, 120 mm. Hg; CO_2, 25 mm. Hg) to those in mixed venous blood (O_2, 40 mm. Hg; CO_2, 48 mm. Hg). It has long been known that reducing the O_2 tension from 150 to 75 mm. Hg has little effect in retarding the growth of tubercle bacilli,[17] but Kempner found that this did reduce metabolic activity of the culture nearly 40%.[18] However, when Rich and Follis kept inoculated guinea pigs in atmospheres low in oxygen they did observe marked retardation of the evolution of tubercles at tensions equivalent to those at 18,000 feet, but there were no retarding effects, as compared with the controls, at tensions equivalent to 14,000 feet altitude.[19] Observations on man would suggest that the alveolar O_2 tensions in the guinea pigs in atmospheres which retarded tuberculosis probably were below 70 mm. Hg (normal, 100 mm.).

Davies grew tubercle bacilli at normal O_2 and constant pH levels but varied the CO_2 tension.[20] He found that growth occurred faster at 25 mm. Hg tensions of CO_2 than in room air (less than 1 mm.) but that growth rates fell 25% below this maximum when the tension was raised to 40 mm. Hg (that of alveolar air) and 40% below maximal at the tension of CO_2 in mixed venous blood (48 mm. Hg). Such data explain why tuberculosis flourished in guinea pigs at O_2 tensions equivalent to those at 14,000 feet, for such atmospheres stimulate ventilation, lower alveolar CO_2 tensions, and thus diminish whatever retarding effects normal CO_2 levels of alveolar air may have on the tubercle bacillus. To study the effect of changing alveolar gas tensions on the evolution of experimental tuberculosis, it would be necessary to use atmospheres enriched with CO_2 as well as impoverished in O_2.

The observations made by Scott, Hanlon, and Olson * on monkeys, together with facts just cited, seem to point to changes in CO_2 tension, in the lobes with altered blood supply, as the factor which most favored the growth of tubercle bacilli and rapid evolution of tubercles. Dubos [21] has shown that high CO_2 levels augment the lethal effect of very low O_2 tensions on Myco. tuberculosis. He also noted [22] that substances normally found in the tissues, such as spermine, retard growth of tubercle bacilli when present in cultures in concentrations in the range found in tissues. In the tissues, it appears that tuberculosis is favored by changes in CO_2 tension such as must occur when pulmonary arterial blood is diverted from a part of the lung.

Scott's observations and the scanty data on the effects of O_2 and CO_2 tension on the metabolism and growth of tubercle bacilli give plausibility to the theory stating that apical localization in human tuberculosis is based on the cessation of apical blood flow when we are in the upright position. But such a theory must be

* References 10-12.

supported by evidence that changes in posture actually do modify the alveolar gas tensions to an extent which might parallel that which must occur in the lobes of monkeys after creating shunts or cutting off pulmonary arterial inflow.

As long ago as 1941, it was reported that oxygen uptake is relatively low in the upper lung when subjects are in lateral decubitus.[13] These studies, made with the bronchospirometer, have been confirmed. Even the 12 to 15 cm. difference in mean hydrostatic pressure between the two lungs when we lie on either side reduces oxygen uptake from the upper lung. In the most recent study of this phenomenon, the change in tidal ventilation was minimal when the patients changed to the lateral decubitus.[14] However, there was a sharp fall in rate of oxygen uptake from the upper lung, such as would occur if part of the lobe was not being perfused with unsaturated blood. In six patients the average proportion of the total oxygen uptake accounted for by the left lung fell 24% when the patients moved from supine to right lateral decubitus, and that of the right lung fell 31% when they were in the left lateral position. Presumably in either case the axillary part of the upper lung receives no blood. Because the pulmonary bifurcation lies 2 to 3 cm. to the left of the midline, the hydrostatic pressure opposing arterial inflow affects a layer of the right lung 4 cm. thicker than that involved on the left, when either lung is above the heart in lateral decubitus. Hence, the right lung shows proportionally greater changes than the left on changing from supine to lateral positions.

Sampling alveolar air with fine bronchial catheters placed far out in the periphery under roentgen control has only recently been accomplished.[15] Apical alveolar tensions were even more "venous" than those at the base in recumbent subjects but were much less "venous" than basal alveolar air when the subjects were sitting up. In the latter posture, apical alveolar air had an O_2 pressure 15% higher and a CO_2 pressure 11% lower than air from the basal alveoli. In the recumbent posture, the apical O_2 pressure was 8% below that in basal alveoli; the CO_2 pressure was 8% higher. This difference is due to the more effective ventilation of the lung close to the diaphragm. Thus there no longer is any reason to doubt that a difference in respiratory gas tension exists between parts of the lung lying well above the center of mass of the right ventricle and those which lie closer to or below the ventricle.

This phenomenon is the inevitable result of the fact that mean pressure at the base of the pulmonary artery normally is less than 20 cm. of blood (15 mm. Hg). In some normal subjects this mean pressure is as low as 14 cm. of blood. With normal pulmonary arterial resistance there is a fall of 6 to 8 cm. pressure between the main artery and the arterioles. Thus, the head of pressure needed to keep the pulmonary capillary circulation going is balanced by a hydrostatic pressure provided by as little as 6 cm. of blood in some subjects and by 15 cm. of blood in nearly all normal persons. The bronchospirometric studies suggest that arterial inflow is regularly reduced in the alveoli lying only 8 or 10 cm. above the pulmonary artery, whether we lie on either side or are sitting up.

This effect of posture is maximal in the apical third of the lungs of adults in the usual sitting or erect postures. Because we tend to "slump" forward, the dorsal parts and the upper poles of the lower lobes are more affected than the ventral part of the lungs. Much more lung tissue is ischemic in tall subjects than in those with short thoracic cages. A very large proportion is affected in those who, because of pulmonic stenosis, have mean pulmonary arterial pressures as low as 8 cm. of blood.

On the other hand, posture can have little or no effect on pulmonary flow in any part of the lungs of those whose mean pulmonary arterial pressures are over 30 cm. of water.

Because the left pulmonary artery, the left upper lobe artery, and the main pulmonary artery follow the line of ejection of blood from the conus, there is little loss of the head of pressure due to turbulence of flow around corners as blood goes toward the left apex. However, the right pulmonary artery turns at an acute angle at the bifurcation, and the upper lobe branch turns at an acute angle at its origin. Thus the pressure head will be lower in the right upper lobe than in the left and the zone of lung with high O_2 and low CO_2 pressures will extend more deeply on the right side than on the left.

It now appears that purely hydrodynamic factors can explain why the number of initial lesions is 50% greater in the right upper lobe than in the left. That such a difference in flow toward the apices of the two lungs really exists was made apparent in a recent case on our wards. A transient pneumonitis followed oil embolism in a young woman who received estrogen in oil, injected into a vein of the buttock accidentally. She was standing up at the time of the injection and for many minutes thereafter. While symptoms were minimal and the x-rays cleared in a few days, the films taken within 36 hours showed densities in both lungs, beginning 4.5 cm. below the apex on the left but 7 cm. down on the right. A similar case, previously reported,[23] showed only the lower halves of both lungs to be altered. In ours, more lung was involved, but more was spared on the right side than on the left. Differences between apical and basal filling of pulmonary arteries can be seen in normal angiocardiograms, taken with the subjects erect, but in these the weight of the column of blood is greatly increased by iodine. In oil embolism no such objection can be raised, and the failure of pulmonary arterial blood to enter the cephalad parts of the lung is clearly shown (Figs. 1 and 2).

The work of Scott, establishing the fact that tuberculosis is favored when the alveolar air is made more "arterial," and the observations on the effects of posture in increasing "arterialization" of the alveolar air in the parts of the lung lying 10 or more centimeters above the pulmonary valve provide support for the theory that hydrostatic and postural influences on pulmonary arterial flow can cause apical localization of tuberculosis in men with massive immunity to infection of the basal two-thirds of the lungs. This theory has been challenged on another basis; namely, that it is hardly compatible with "the great frequency with which tuberculous lesions develop in the infraclavicular region, rather than at the extreme apex."[3] This criticism would carry great weight if the apical lesions were less frequent and if the infraclavicular region was the same volume as the apex. Above the second costal cartilage, all the lung is at a level where pulmonary arterial pressure cannot maintain blood flow in normal subjects sitting erect. But since the lobes are cone-shaped, the volume of lung in a layer of given thickness is only one fourth as great at the midclavicular level as in a similar layer at the upper edge of the second rib at the manubium. The hydrostatic theory would have to be abandoned if lesions below the clavicle actually occurred more often, per gram of lung, than those at the apex.

In Medlar's study of minimal active lesions, disclosed during necropsy in 1,200 cases of sudden or violent death,[24] there were 44 active lesions above the lower edge of the clavicle, 37 above the third costal cartilage but below the clavicle, and only

31 in the rest of the lung. Thus there can be no doubt that, per gram of lung, active apical lesions are much more numerous than the subclavicular ones. In this definitive study of early progressive tuberculosis Medlar found active lesions on the right side predominating three to two in the upper third of the lungs. This fits the data which indicate that the ischemic zone is larger on the right side because of the tortuous course of the artery. In the lower parts of the lung lesions were often found near the axilla, with 17 on the left side and 14 on the right. Since people tend to lie on the right side much more than on the left, the region near the left axilla will have the longest periods of ischemia during sleep, as has been shown by the studies on gas exchange on the two sides in lateral decubitus.† This will favor the growth of tubercles on the left side in the lower halves of the lungs. It therefore appears that all Medlar's observations on localization in cattle, in rabbits, and in men can be explained by the postural, hydrostatic, and gas tension differences,

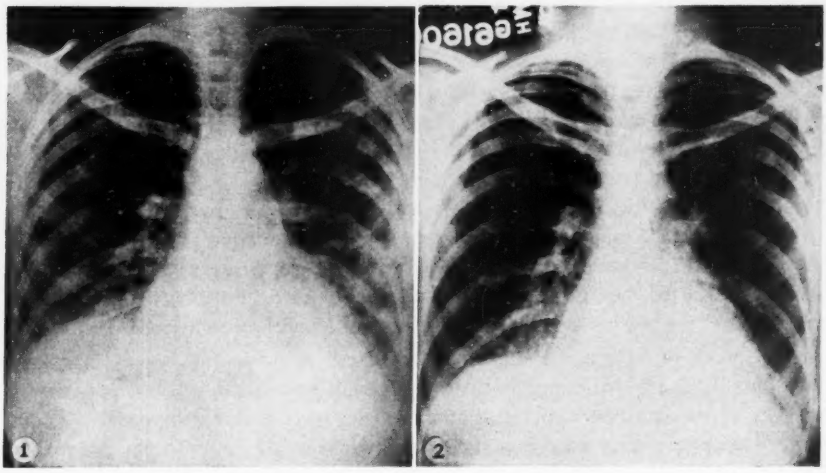

Fig. 1.—The initial chest films after sudden onset of respiratory symptoms due to oil embolism from an intragluteal injection given with the subject standing. Infiltrations extend to within 4 cm. of the left apex, but are absent in the cephalad 7 cm. on the right. This presumably is due to the lower pressure head on the right side, owing to the tortuous course of the artery.

Fig. 2.—Same subject, four days later, after all symptoms had cleared and infiltrations had been reabsorbed.

while none of the facts can be explained in any other way. However, Medlar has stressed the fact that even at the apices the ventral part of the lung is spared, while the upper parts are affected most frequently in the lower lobes as well as in the upper,[24] and others have claimed that the upper half of such organs as the kidney and liver also seem to be more favorable sites for progressive lesions.[16]

It is not remarkable that the apical localization of tuberculosis has been ascribed not only to influences which retard or favor the growth of tubercle bacilli but also to those which might affect the planting of the foci in the first place. Such influences are of great importance in determining the sites of pyogenic infections, reach-

† References 13 and 14.

ing the lungs by way of the bronchi, or septic infections, or emboli borne by the blood. Medlar's study [24] confirmed previous work in showing that primary complexes, generally conceded to be due to air-borne bacilli entering the bronchi, are scattered at random throughout all areas of the lung. Everywhere these tend to heal, but the proportion which becomes progressive was shown in his studies to be far greater at the apices than elsewhere. This fits with the great immunity of the basal regions to infection in patients with open apical lesions and enormous numbers of bacilli in the bronchi and with the more rapid growth of disseminated miliary lesions at the apices than at the bases of the lungs.‡ Apical localization is due to favorable soil, not to heavier seeding of tubercle bacilli.

The solution of this problem, which has stirred the curiosity of medical students since Laennec aptly described the remarkable anatomical facts, is not without practical importance. It provides a rational explanation for the low incidence of lesions in mitral stenosis, the high incidence in pulmonic stenosis,[25] and the effectiveness of lying flat in bed for the arrest and healing of early apical tuberculosis. It also explains the refractory state which is seen with chronic cavitation. These chronic inflammations evoke the development of a rich bronchial arterial supply, as demonstrated by Wood and Miller [26] and others. This creates the same situation as that seen in monkeys with shunts from the systemic to the pulmonic artery. In these arterialized zones, posture will not change gas tension. Bed rest, though protecting adjacent lung or the opposite apex, no longer will retard growth of bacilli in the richly arterialized lesions. Also, it is apparent that the value of bed rest for long periods of time has been greatly modified by the development of antibiotics. When therapy is started, bed rest is of some value in assuring maximal antibiotic levels at the site of the lesions by improving pulmonary blood flow to all parts of the lung.

The work of Rich and Follis, showing arrest of guinea-pig lesions in animals breathing 10% oxygen,[19] proved that changing alveolar gas tension was effective in spite of the constant hyperventilation which anoxia induces in such an experiment. Lesions were retarded in spite of "overwork" of the lung. In patients, change in alveolar gas tension is far more important than "rest" for the lung. When we are recumbent the bases are ventilated better than the apices, but this "work" does them no harm. Collapse of a lung causes the maximal possible change of alveolar gas tension, and it is now evident why pneumothorax or thoracoplasty are so effective, since collapse greatly reduces blood flow,[27] and changes pulmonary O_2 and CO_2 to the levels in venous blood.

Strains of bacilli resistant to known and yet-to-be discovered antibiotic combinations may appear, but strains which are insensitive to the tension of gases in venous blood are not known. The tubercle bacilli has made no progress in this respect in the two and a half centuries since Valsalva pointed out to his colleagues that the lesions were found "in the upper lobe."

While tuberculosis can be eliminated from any prosperous country, and the death rate is falling fast in North America and Scandinavia, it still remains, even in these countries, the chief cause of disability and death of those in the prime of life. In the far larger and more populous parts of the globe where living standards

‡ Reference 3, pp. 782-784.

are low, with rapidly increasing populations and chronic malnutrition, tuberculosis probably will long remain the chief cause of death of those who survive through infancy.

The industrial revolution, with cheap artificial light and greatly lengthened working hours, gave tuberculosis its great harvest in Western Europe and North America. The totalitarian states have created new favorable soil by increasing the rate of urbanization and industrialization all over the world. Throughout most of our globe tuberculosis remains the Captain of the Men of Death, as it was entitled by John Bunyan, a contemporary of Valsalva and Morgagni. In their day, cholera, plague, typhoid fever, syphilis, and lobar pneumonia were still tremendous killers of those in the prime of life. These have almost vanished, and tuberculosis remains unrivaled. Thanks largely to Medlar and work his observations inspired, we now can account for the vulnerable spot in the armor which so effectively protects most parts of our bodies and even of our lungs. With this knowledge, with antibiotics, and with methods for early detection, the fight against the Captain of the Men of Death can be fought with far better odds than were conceived possible only a generation ago.

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NEPHROSIS AND FAT EMBOLISM IN ACUTE HEMORRHAGIC PANCREATITIS

MATTHEW J. LYNCH, M.D., M.R.C.P. (Lond.)
With Technical Assistance of Les D. Mellor, F.I.M.L.T., R.T.
SUDBURY, ONT., CANADA

IN THE past 18 months personal autopsy examination and histologic study have been made on four cases of florid acute hemorrhagic pancreatitis, on one case of focal acute hemorrhagic pancreatitis, and on one case showing sequelae of a severe remote attack. In all acute cases I have been deeply impressed by the degree and extent of renal nephrotic involvement. This seemed to be so much an integral part of the syndrome that it appeared to have some common etiologic basis, and the study here recorded is believed to elucidate the nature and cause of the renal involvement and to emphasize a possibly common fatal complication of acute hemorrhagic pancreatitis. In addition, it is believed that the "chronic," or remote, case hereunder described completes the picture of the natural course and evolution of the renal lesion in those who survive the acute episode.

REPORT OF CASES

The Acute Phase

Case 1.—A. C., a white man of Greek stock, aged 62 years, was hospitalized 48 hours after the onset of severe epigastric pain accompanied by nausea and vomiting. On admission his serum amylase was 664 Somogyi units; blood sugar, 213 mg. per 100 ml.; the direct Van den Bergh reaction was positive, and the total serum bilirubin was 3.6 mg. per 100 ml. Urinalysis at that time showed pH, 7.0; specific gravity, 1.026; proteinuria, 2+, and, on microscopic examination, moderate numbers of hyaline and granular casts.

On conservative management the patient's condition progressed satisfactorily for five days, but on the sixth day of hospitalization it began to deteriorate. Cyanosis and rapid, shallow respirations developed, and some confusion of intellect, unresponsiveness, stupor with grunting respirations, and finally, coma appeared. On the 10th day after admission, when coma developed, the serum amylase was down to 105 units; the blood sugar was 480 mg. per 100 ml.; blood nonprotein nitrogen was 72 mg. per 100 ml., and the CO_2-combining power of the plasma was 44 vol. %. On that day tracheotomy had to be performed because of right-sided parotitis and a spreading type of Ludwig's angina. Though there was no acetone in the urine, insulin (50 units every four hours) was given. Pyrexia set in on the ninth day of hospitalization and increased steadily to a peak (temperature of 107 F.) two days later, when the patient died in coma, 13 days from the onset of his disease.

Autopsy Examination (S. G. H. A65/54).—Permission was restricted to examination of chest and abdomen. Autopsy, performed within two hours of death, on this obese pale elderly man, revealed the lower lung lobes to be partially collapsed, though the lungs, generally, were congested and showed minute indistinct grayish-red areas throughout. The gall bladder was

From the General Hospital.

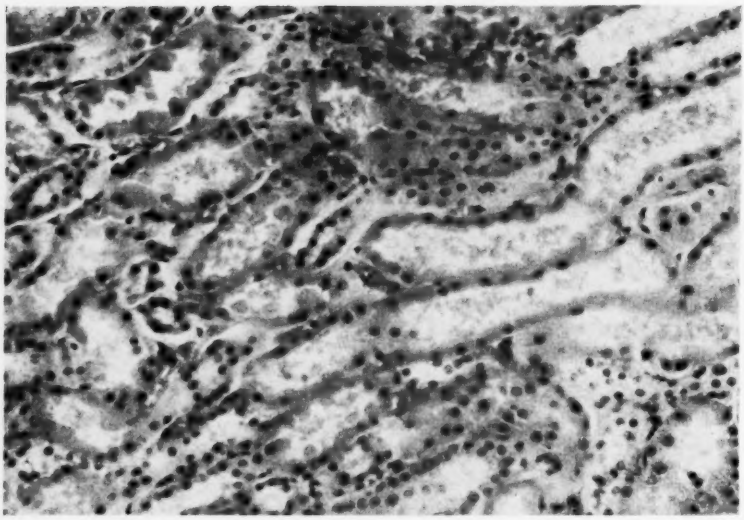

Fig. 1 (Case 1).—Kidney, showing widespread tubular degeneration. Hematoxylin and eosin; × 300.

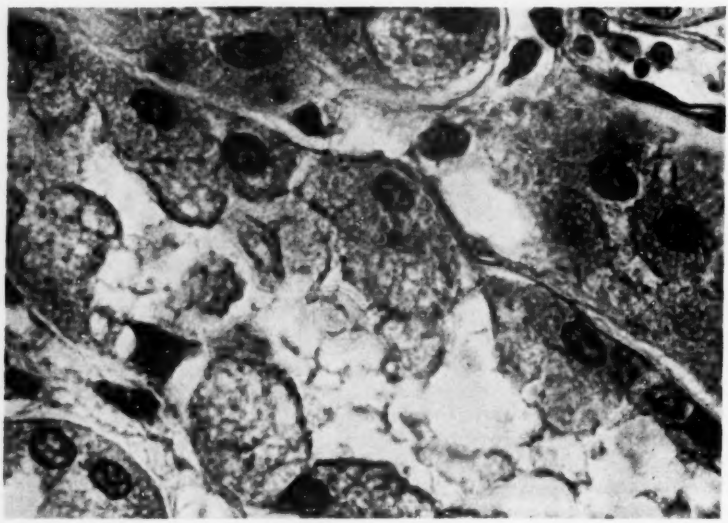

Fig. 2 (Case 5).—Kidney, showing severe tubular epithelial degeneration, vacuolation, swelling, and shedding. Hematoxylin and eosin; × 1,260.

distended with bile of normal appearance and showed many small (2 mm. diameter) circular shallow blackened erosions of the mucosa. The common bile duct was dilated, but no stones or sludge were present in either gall bladder or bile ducts. The pancreas was surrounded by a thick mass of fat showing widespread and heavy chalky deposits. Along the upper half of the pancreas there was a thick band of mushy brown necrotic and hemorrhagic material, and a similar material occupied about half of the head of the organ. The kidneys were normal in size. Their capsules stripped easily, leaving pale cortical surfaces. The cut surfaces displayed marked pallor, and the cortices bulged slightly.

Histopathology.—Hematoxylin-and-eosin-stained sections confirmed acute hemorrhagic pancreatitis with widespread necrosis of interlobular and surrounding fat. Routine sections of the lungs revealed passive congestion and edema, with abundant small foci of bronchopneumonia. The erosions seen in the gall-bladder mucosa were of subacute nature, and large numbers of macrophages were present in the bases of these ulcers. The liver sections revealed marked centrilobular fat vacuolation of parenchymal cells. The microscopic picture of hematoxylin-and-eosin-stained sections of the kidneys was one of intense epithelial damage in the convoluted tubules. Most cells of these tubules were enormously swollen and tattered and were granular and foamy; disruptive degeneration of their cytoplasm was universal. Indeed, the inner parts of many cells had been shed into the tubular lumina, where they lay as granular eosinophilic debris. In many cells, also, the nuclei were pale-staining and ghost-like, and they had disappeared completely in a number of cells. These changes were the more remarkable and significant since the autopsy was performed within two hours of death and fixation was effected as thin (2 mm. and less) slices of tissue in 10% formol and saline solution.

In frozen sections, staining by Sudan IV followed by Mayer's hematoxylin stain revealed widespread fat embolization. In the lungs this was found most frequently in association with the small pneumonic areas. In the kidneys fat emboli were seen in the capillaries of the glomerular tufts and in the efferent and intertubular arterioles and capillaries. Fat droplets, both large and small, were seen in the tubular lumina, and massive fat-vaculolation was seen in the epithelial cells of the convoluted tubules. Though no fat emboli were demonstrable in the gall-bladder wall, the macrophages in the bases of the mucosal erosions were seen to contain many small fat vacuoles. In the extant areas of pancreas the interlobular zones were laden with fat-filled macrophages, and many vein-like vascular channels in the acinar lobules were filled with fat. The preparation of frozen sections from the necrotic areas of pancreas was extremely difficult but most rewarding. In the fatty tissue bordering on and in these sites only very few fat cells were seen to contain stainable neutral fat. However, in the desolate areas of necrosis small and large lakes of neutral fat were commonly found, and the vascular spaces leaving these zones were frequently laden with fat. On two occasions neutral fat was seen oozing through a vein wall as small droplets from a contiguous pool of fat.

The Chronic Renal Lesion

Case 2.—Mrs. P. S., in 1941, when 16 years of age, developed a tumor on the posterior aspect of her right scapula. This was removed in Saskatoon in November, 1943, and local irradiation was given at the Mayo Clinic, where a diagnosis of malignant endothelioma was made. In July, 1944, she developed a recurrence in the supraspinatus muscle. Biopsy was performed in Winnipeg, and pathologic diagnoses of synovioma and rhabdomyosarcoma were offered. However, the patient refused further operation until May, 1945, when a partial excision of the right scapula was performed in Winnipeg. Following this the patient remained well until May, 1952, when local recurrence again occurred. Dr. H. F. Mowat removed a mass of tumor 3 by 2 by 1½ in. (7.5 by 5 by 3.7 cm.) from the right supraspinatus fossa in September, 1952, at The General Hospital, Sudbury. Local roentgen therapy was then given and was repeated in March, 1953. Evidence of rib and spinal metastases then appeared, and progressive anemia and deterioration set in, and the patient finally died on Dec. 9, 1953. No record of any illness simulating acute pancreatitis appeared in the patient's notes, though in the last nine months severe girdle pains were a constant feature of her complaint.

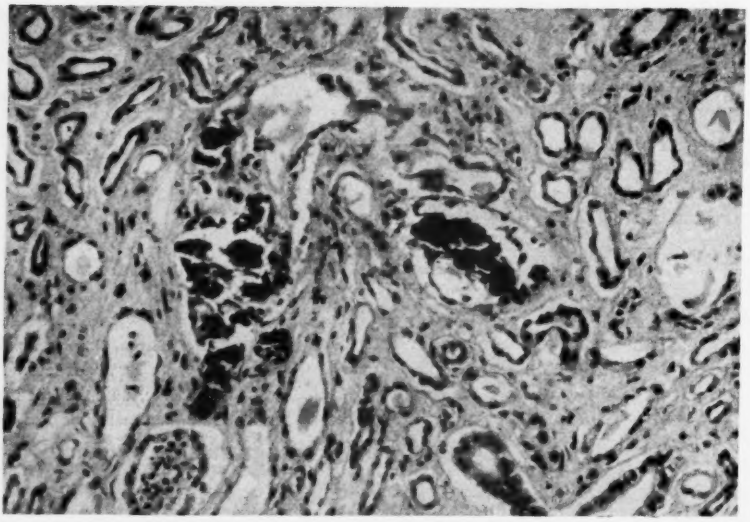

Fig. 3 (Case 2).—Kidney. View of cortex, showing gross tubular degeneration and atrophy, hyaline casts, interstitial fibrosis, and calcium deposits. Hematoxylin and eosin; × 300.

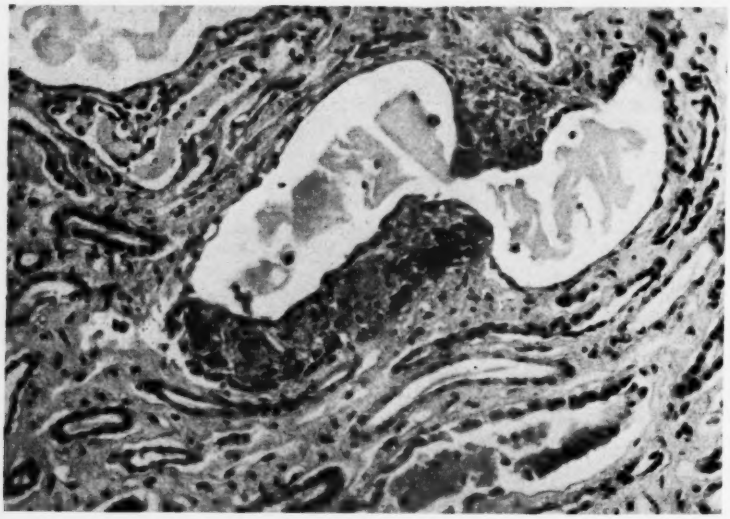

Fig. 4 (Case 2).—Kidney, showing tubular atrophy and dilatation, casts, interstitial fibrosis, and granular juxtatubular calcification. Hematoxylin and eosin; × 300.

During her illness the investigations bearing on her renal function were, unfortunately, very scanty. However, from May, 1953, repeated urinalyses on fasting morning specimens showed the specific gravity to vary between 1.013 and 1.015, while traces of protein and granular casts were recorded from time to time. In May, 1953, her total serum proteins were 6.7 gm. per 100 ml., albumin being only 2.28 gm. and globulin, 4.5 gm. per 100 ml.

Autopsy Examination (S. G. H. A102/53).—The essential findings were those of metastases to the pleurae, lungs, adrenals, and bone marrow. Four nodules of tumor, each about 2 cm. in diameter, were present in the liver. Sections showed a malignant endothelioma. No tumor deposits were found in the peritoneum or in the neighborhood of the pancreas. The abdominal cavity, however, showed the finest possible example of old fat necrosis. Omentum, mesentery, and pelvic peritoneum were almost completely encrusted with white chalky material of egg-shell and granular consistency. These deposits were most dense about the pancreas; indeed, the whole of the somewhat shrunken pancreas appeared to be encased by this chalky material. The gall bladder

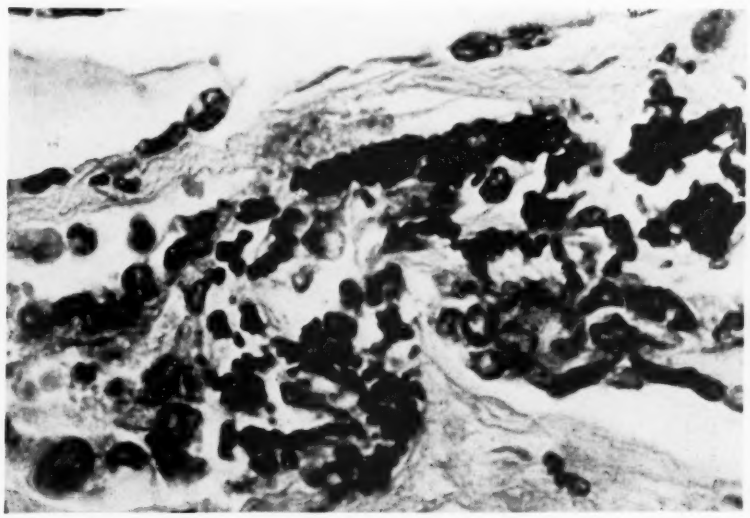

Fig. 5 (Case 2).—Kidney, showing granular calcification between tubules, which are greatly distorted. Hematoxylin and eosin; × 1,260.

and biliary tract were normal, and no stones were present. The renal capsules showed punctate adhesions, but they stripped with moderate ease, and the resultant capsular surfaces did not appear significantly abnormal. The cut surfaces of the kidneys showed only pallor, and the calyces, pelves, ureters, and bladder were normal.

Histopathology.—Sections of pancreas showed residual chronic interstitial inflammation, with focal lobular obstructive acinar atrophy. The fat on the surface and between lobules was almost completely replaced by calcium salts, which also constituted the peritoneal deposits. As far as could be judged, the acute phase of the pancreatitis must have been from two to nine months prior to death. The kidneys displayed pronounced and widespread pathologic changes. There was a tremendous over-all increase in interstitial connective tissue, without any evidence of even minimal inflammatory response and obviously at the expense of the tubular structure. The glomeruli, while not appearing as severely affected as the tubules, showed a general reduction in size, diminished numbers of capillary tufts, and a sensible increase in intercapillary ground substance. The convoluted tubules were severely reduced in number and revealed a universal and

striking change in character. Their epithelia were all of low-cuboidal, atrophic nature, and the lumina of some were grossly dilated in an irregular manner, while many contained eosinophilic hyaline casts. The most striking and significant finding, however, was that of coarse granular calcium deposits just outside tubular basement membranes and between closely set tubules, i. e., in the site of the tubular capillaries. Indeed, in many areas long streaks of this calcium deposit could be seen between closely apposed tubules, and in some cases minute vascular channels were seen emerging from and entering and being lost in the calcium deposits. This paratubular calcium deposition was seen throughout both kidneys but appeared most abundant in the vicinity of the convoluted tubules.

Other Personally Studied Autopsies Showing Hemorrhagic Pancreatitis and Nephrosis

Case 3 (R. A. H. A74/53).—Mr. K., aged 35 years, died on the third day of acute hemorrhagic pancreatitis which had its onset during a bout of alcoholism. Routine kidney sections

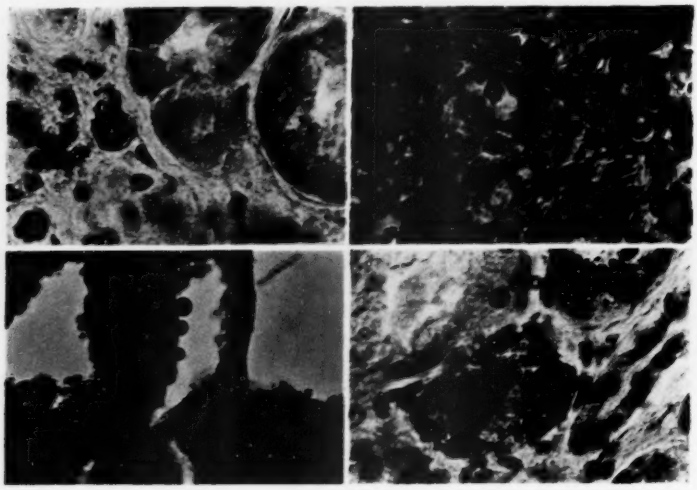

Fig. 6 (upper left).—Kidney. Frozen section, showing fat embolus in intertubular capillary. Ektachrome transparency; Sudan IV and Mayer's hematoxylin stain; × 420.

Fig. 7 (upper right).—Kidney. Frozen section, showing fat emboli in glomerular capillaries. Ektachrome transparency; Sudan IV and Mayer's hematoxylin stain; × 420.

Fig. 8 (lower left).—Pancreas. Frozen section of necrotizing area, showing fat oozing as droplets into a venous channel from an adjoining lake of fat, which is not in focus, as it is in a deeper plane. Focusing at deeper plane revealed innumerable minute bubbles of fat directly continuous with the extramural pool of fat. Endothelium and laked red corpuscles were seen in the vascular channel. Ektachrome transparency; Sudan IV and Mayer's hematoxylin stain; × 420.

Fig. 9 (lower right).—Kidney. Frozen section, showing fat droplets in degenerating and damaged tubular epithelium and lumina. Ektachrome transparency; Sudan IV and Mayer's hematoxylin stain; × 420.

All Ektachrome transparencies are from Case 1.

showed a most severe nephrosis, the whole tubulature being virtually obliterated, as in the case of Wilkey and co-workers.[1]

Case 4 (R. A. H. A102/53).—Mrs. S., aged 59 years, developed acute hemorrhagic pancreatitis of the tail of the pancreas, due to arterial embolism from rheumatic mitral stenosis with auricular fibrillation. Sections of kidneys revealed a severe nephrotic lesion.

Unfortunately, material from Cases 3 and 4, which were autopsied by me in Edmonton, is not available for further study.

CASE 5 (S. G. H. A30/54).—Mrs. M. L., aged 40 years. Urinalysis, performed six hours after the onset of acute abdominal pain with dyspnea and cyanosis, showed proteinuria and moderate numbers of granular and cellular casts. She became progressively more restless and irrational and deeply cyanosed, and she died eight days after the onset of her illness. Autopsy examination disclosed severe acute hemorrhagic pancreatitis, with extensive fat necrosis in mesentery and retroperitoneal areas. Numerous gallstones were found in the common duct. Histologic examination revealed severe nephrosis, and frozen sections stained by Sudan IV followed by Mayer's acid alum hematoxylin stain showed moderately heavy fat embolization of kidneys, lungs, and heart.

CASE 6 (S. G. H. A71/53).—Mr. I. D., aged 64 years, died of multiple metastases from anaplastic carcinoma of bronchus. Autopsy also revealed a focal acute hemorrhagic pancreatitis involving only about one-tenth of the organ. Sections of kidneys revealed a slight nephrotic picture, such as might have been attributable to delay in fixation of tissues. Fat studies were not made.

COMMENT

Search of the literature has failed to reveal any record of a similar study. Wilkey and co-workers [1] have described a case of acute necrotizing pancreatitis and lower nephron syndrome following transurethral prostatectomy. They attributed the nephrosis to activated proteolytic enzymes presumed released from the prostate, but they admitted that they were quite unable to explain the 10-day time lag between the prostatectomy and the onset of the acute pancreatitis. However, they stressed their conviction that a common or connecting factor underlay the pancreatitis and the nephrosis. These authors mention three similar cases in the literature. Gaberman and co-workers [2] list the renal anoxic syndrome as occurring in acute pancreatitis. However, many recent reviews of acute hemorrhagic pancreatitis do not even mention renal complications, e. g., Gambill and co-workers,[3] though others are aware of a common but poorly defined impairment of kidney function, e. g., Berk.[4]

The studies here recorded suggest that the chief connecting link between acute necrotizing pancreatitis and the commonly associated nephrosis is that of fat embolization. It is my contention that this leads to ischemic nephrosis directly proportional to the degree of fat embolization and, thereby, probably equally proportionate to the severity of the pancreatitis and degree of obesity of the subject.

I have long felt that the cause of death in acute hemorrhagic pancreatitis has been too vague and inadequately explained. Now, however, I am unable to escape the conclusion that death occurs from either fat embolization or nephrosis or from both. Unfortunately, I have been unable to study the brains of these cases for fat embolism. In this connection, I think it pertinent to recall the paper by Vogel,[5] who described cerebral demyelination and focal visceral lesions in a case of acute hemorrhagic pancreatitis. Vogel was unable to demonstrate fat emboli in the brain and lungs, but, apparently, he did not study other organs by frozen section technique and fat stains. However, the pyramidal-shaped necrotizing areas in the ovaries of his case and the necrotic lesions in the heart and adrenals suggest an infarctive process. Vogel's failure to demonstrate fat emboli in the brain or lung of his case may well be explicable on the basis of time. It is noted that his paper gives no indication of how long the pancreatitis existed before death. In my opinion this time factor may be critical, for it is logical to assume that in such a disease, with a high circulating lipase titer, fat emboli may be split so that they will not take neutral

fat stains. Indeed, I can not help believing that far heavier fat embolization will be found in those dying early in the disease, e. g., in the second to fifth days.

The natural evolution of this fat-embolic ischemic renal lesion would seem to be well illustrated in Case 2 of the present series. It is natural to expect that such a lesion will produce an ischemic, aseptic, and almost noninflammatory lesion leading to tubular atrophy and replacement interstitial fibrosis. The ameboid fat globules may be expected to be pushed gradually onwards from the high pressure areas of the afferent arterioles and glomerular tufts into the relatively low-pressure beds of the efferent arterioles and intertubular capillaries. This may well lead to a preponderance of tubular over glomerular lesions. Of course, a few glomerular tufts may be obliterated, but a similar degree of embolization of a nephron's vasculature, if it moves onwards or gets through the glomerular tufts or shunt-by-pass, will produce a far more noticeable and greater ischemic damage to the tubulature of the affected nephron.

Most cases probably die at or before this stage from the effects of embolization of lungs, heart, or brain. Indeed, the cyanosis which commonly accompanies severe acute hemorrhagic pancreatitis is probably attributable to fat embolization of the pulmonary capillary bed. In those who develop and survive fat embolization, the fat emboli in the kidney may be split by lipase and disappear. However, due to the local relative or absolute ischemia, splitting is probably more often delayed. It is natural to assume that a gradual deposition of calcium will occur in the embolus. Hence, the end-result may be, as in Case 2, interstitial fibrosis, moderate glomerular shrinkage, severe degeneration of the convoluted tubules, and granular calcium deposition on and in the embolized arterioles and capillaries, giving rise to a kidney which gradually leaks plasma albumin, owing to glomerular damage, and forms a urine of fixed medium specific gravity by virtue of tubular impairment.

It is, of course, quite possible and even probable that the acute embolic, ischemic renal lesion is aggravated by circulating enzymes and toxic tissue products. Indeed, the uniformity of the nephrotic damage would appear to indicate such an auxiliary factor, though the heavy, widespread fat embolization must be the main culprit. As to the frequency with which fat embolism of significance occurs in acute hemorrhagic pancreatitis, I do not feel qualified on the extent of the present work to offer more than a guess that it is of common occurrence.

The question naturally arises as to how soon in the course of the disease fat embolism begins and for how long it continues. I believe that it may begin within a few hours of the onset of the disease, i. e., as soon as the peripancreatic and interlobular fat begins to be split in any quantity and to ooze its way through vascular walls damaged by the enzymes liberated. Anyone who has given more than cursory study to routine sections of the pancreas in this disease will have noted the obvious and widespread swollen and fuzzy appearance of both venous and arteriolar walls, even in areas of pancreas showing relatively little damage. As to the duration of active fat embolization, it may be noted that in Cases 1 and 5 of the present study fat embolization was moderately heavy and widespread 13 and 8 days, respectively, from the onset of the pancreatitis. With some inaccuracy we may take serum calcium levels as a rough guide to the duration of the active fat embolism, which may, therefore, be assumed to continue in some cases for as long as 14 days, though it must be obvious that the major embolization must occur from the second to the fifth days.

The explanation of the heavy fat vacuolation of the damaged tubular epithelium must at this stage be little more than speculative. Frozen sections stained by Sudan IV and Mayer's hematoxylin stain certainly suggest that fat escapes through the glomerular tufts. Whether the epithelium of the convoluted tubules attempts to absorb this fat, or whether their own damaged condition causes fat to be unmasked, one can not say definitely. However, the great amount of fat in some of the cells would suggest that absorption plays at least a part in the picture.

SUMMARY

One case of acute hemorrhagic pancreatitis is described in full; three similar cases are briefly outlined, as is also one case of focal acute pancreatitis of necrotizing type. In all cases pronounced nephrosis was a striking pathologic finding. Two of the acute cases were investigated by frozen section fat-stain technique, and widespread fat embolization was revealed. This is believed to be the cause of the commonly occurring nephrotic renal damage in this disease, though it is conceded that circulating enzymes and toxic tissue products may contribute.

A sixth case is described, in which sequelae of a remote attack of acute hemorrhagic pancreatitis were found. In this case severe interstitial renal fibrosis, tubular atrophy, and paratubular granular calcification are believed to represent the natural evolution of the acute renal lesion in hemorrhagic pancreatitis. However, it is likely that very few cases reach this end-stage.

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MANAGEMENT OF PATIENTS WITH MITRAL STENOSIS BEFORE, DURING, AND AFTER MITRAL VALVULOPLASTY

GEORGE N. BEDELL, M.D.
PHILADELPHIA
JAMES W. CULBERTSON, M.D.
AND
JOHANN L. EHRENHAFT, M.D.
IOWA CITY

IT IS NOT the province of this paper to discuss in detail the diagnosis of mitral valve disease or to delineate our criteria for selection of patients for operation. We have considered the latter problem at a previous meeting of this Association.[1] However, a few statements in this regard may be useful.

At the State University of Iowa Hospitals internists, radiologists, clinical physiologists, and surgeons work as a team (Fig. 1) in the selection of patients for mitral valvuloplasty and in their management. To date 95 cardiotomies have been performed on patients ranging from 11 to 60 years of age, with an operative mortality rate of only 4.3%. We do not recommend operation on patients in whom mitral stenosis exists but in whom there are no clinical symptoms referable to this lesion. All 95 patients have had symptomatic mitral valve disease; many had been deteriorating clinically, and a few had been in chronic intractable heart failure.

The principal contraindication to mitral valvuloplasty is left ventricular hypertrophy, whether from dynamically significant mitral insufficiency, aortic stenosis, aortic insufficiency, or coarctation of the aorta.

PREOPERATIVE CARE

During the 7- to 10-day preoperative clinical and physiological observation period congestive heart failure, if present, is controlled by standard methods (Fig. 2). If digitalis alkaloids have been given preoperatively, they must not be discontinued at this time lest the tendency to cardiac failure and postoperative supraventricular tachycardia be enhanced. A low-sodium diet is continued when it is already in force but is not instituted unless the patient has edema. Quinidine is not given routinely, but in patients who have had bouts of paroxysmal atrial fibrillation or

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From the Cardiovascular Laboratory, the Department of Internal Medicine, and the Division of Thoracic Surgery of the Department of General Surgery, College of Medicine, State University of Iowa.

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who are having frequent premature contractions it is given in dosage of 0.4 gm. four to six times daily prior to operation and for at least one week afterward. Usually no attempt is made to convert chronic atrial fibrillation to a regular sinus rhythm before operation. A conscientious attempt is made to exclude the presence of rheumatic activity and infection, especially subacute bacterial endocarditis, by means of customary clinical methods.

OPERATIVE PROCEDURE

The anesthetic agents employed are not in themselves important. Due to the fact that the surgeons desire the use of electrocauterization, nonexplosive agents are chosen. The usual method comprises nitrous oxide with oxygen by endotracheal tube supplemented by opiates, barbiturates, and/or muscle relaxants. Externally controlled respiration is essential in order to avoid the hypoventilation which tends to occur with an open chest. Care must be taken to avoid circulatory depression either by drug overdosage or by excessive positive pressure within the airway.

An isotonic solution of sodium chloride is administered by slow intravenous drip through 15-gauge needles in the right arm and in one ankle. We feel that having two needles through which large volumes of blood could be pumped rapidly is a necessary safety factor. A supply of 1,500 ml. of properly cross matched whole blood is kept in readiness in the operating room, although usually not more than 500 ml. is used.

Cardiac mechanism is monitored electrocardiographically during the operation (Fig. 3). After the pericardial sac is opened, the epicardium occasionally is bathed with lidocaine (Xylocaine) to reduce its sensitivity if there is evidence of abnormal ventricular irritability. When the surgeon has opened the left atrium, pressure pulse waves are recorded through a catheter before and after manipulation of the mitral valve (Fig. 4). In mitral stenosis left atrial mean pressure always is elevated, usually to levels between 20 and 40 mm. Hg. After successful valvuloplasty there is regularly a drop of from 5 to 15 mm. Hg.

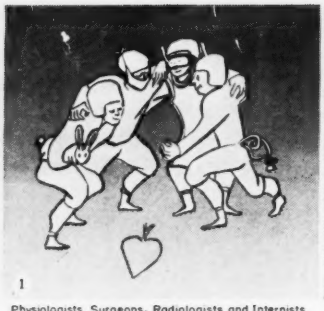
At one time we suspected that mitral insufficiency severe enough to preclude successful valvuloplasty might be diagnosed regularly from pulmonary "capillary" pressure pulse waves recorded through a catheter preoperatively [2] or from left atrial waves recorded through a needle from the intact atrium at thoracotomy.[3] However, after studying tracings from 57 patients, collected over a 30-month period, we have concluded that it is not possible in every case to diagnose significant mitral regurgitation by these methods.* Therefore, the left atrium now is opened routinely at thoracotomy and the valve examined by the surgeon's finger.

IMMEDIATE POSTOPERATIVE CARE

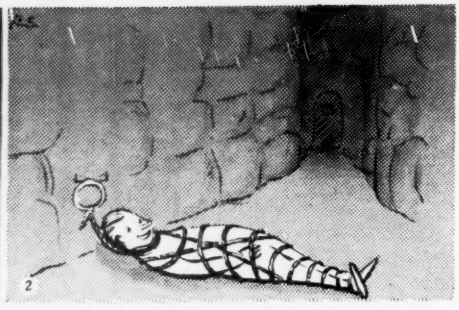
In the early postoperative period patients must be watched carefully for evidence of failure of expansion of the left lung, myocardial decompensation, cardiac rhythm disturbances, and arterial embolism. A roentgenogram is made three or four hours postoperatively to exclude serious pneumothorax. The patients are encouraged to take deep breaths (Fig. 5) and to cough, which they usually are reluctant to do. We attempt to keep them slightly undersedated in the early postoperative period to avoid diminished respiratory excursion of the chest. However, one must be careful to give adequate pain relief, because tachycardia from pain alone is a well-recognized phenomenon which produces a distinctly adverse effect. Chest pain is controlled with meperidine (Demerol) given every three or four hours as needed.

Congestive heart failure is another important immediate postoperative complication, having occurred in 11% of our patients. If decompensation appears, a rhythm disturbance must be suspected (Fig. 6). Our most common arrhythmia has been paroxysmal atrial fibrillation, which we treat promptly and vigorously. First, the cardiac rate is slowed with a digitalis alkaloid if the patient is known to be less than

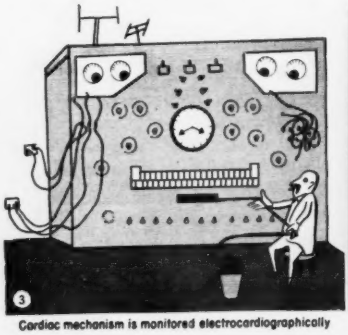
* References 4-6.



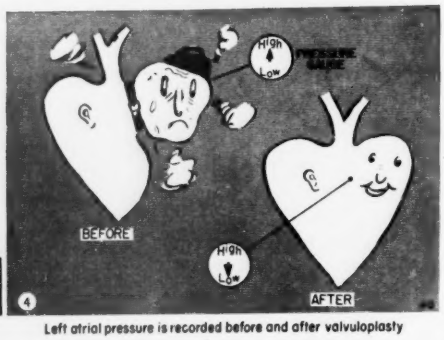
Physiologists, Surgeons, Radiologists and Internists act as a team



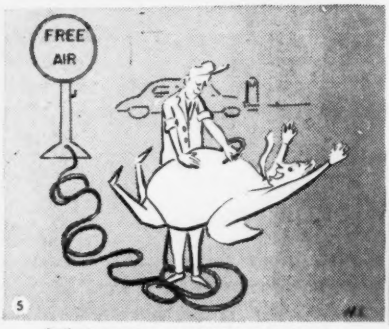
Cardiac failure is controlled



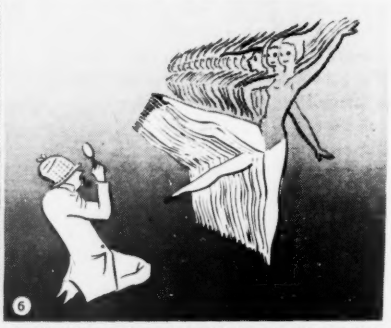
Cardiac mechanism is monitored electrocardiographically



Left atrial pressure is recorded before and after valvuloplasty



Patients are encouraged to take deep breaths



If cardiac failure develops, a rhythm disturbance must be suspected

Illustrated Review of Management

Reactivation of rheumatic fever has not been a problem

fully digitalized. The drug should be given intravenously if the ventricular rate is more than 140 beats per minute. Once the patient has been digitalized completely quinidine sulfate, 0.2 or 0.4 gm., is given orally every two hours for five doses or until prior conversion to a regular sinus rhythm on the first day. Thereafter, if necessary, the individual dose of quinidine sulfate is increased each day by an increment of 0.2 or 0.4 gm. An individual dose of 1.0 gm. is required only rarely and should not be exceeded. Particular attention is paid to signs of quinidine intoxication, and the drug is discontinued if they appear or whenever normal rhythm has been restored. We stress the precaution that the cardiac rhythm should be observed by a physician prior to each dose of quinidine. Occasionally, a rapid supraventricular tachycardia develops in the early postoperative period and requires management by emergency measures. Some patients who have not been on digitalis preoperatively go into heart failure postoperatively and need digitalis for the immediate postoperative period only. In these patients mild decompensation which responds promptly to treatment is not a bad prognostic sign. In one of our patients overwhelming mitral regurgitation developed after operation, severe intractable heart failure developed, and death ensued 10 days later.

Arterial embolization is another important complication of the operation, having occurred in 6% of our patients. Significant peripheral emboli can be removed surgically with excellent results if they are recognized promptly. If peripheral embolism occurs at thoracotomy, the anesthetist usually notes a transient rise in arterial pressure and should report this at once to the surgeon. Prompt embolectomy and antispasmodic and anticoagulant therapy should be considered.

INSTRUCTIONS TO PATIENTS RETURNING HOME

Ordinarily patients leave the hospital 10 to 14 days after operation, and they are discharged to the care of the referring physician. At this time they must be given specific instructions in regard to diet, activity, and medication. Those who did not manifest dependent edema prior to operation are permitted sodium as desired in diets with caloric values appropriate to the individuals' body weights. Those who were in chronic congestive right ventricular failure before operation are advised to practice sodium restriction until their progress has been observed for a few months. In this group a general diet may be allowed later.

Activities should be resumed cautiously. This sometimes poses a problem, inasmuch as the patients' sense of well-being and their ambition may improve dramatically. During the first postoperative month they may be allowed to increase their activity progressively but gradually. Regular rest periods are recommended. When they return one or two months later, careful questioning, examination, and information from the referring physician usually will disclose whether myocardial decompensation or cardiac mechanism disturbance has developed following operation. If progress has been satisfactory, further increase of activity is advised, with caution that it should be kept within the limits of comfortable tolerance. Many patients are able to return to full-time work after one or two months, if they are not employed in strenuous occupations.

When a digitalis preparation has been required preoperatively, it is continued during the immediate postoperative period and maintained upon discharge from the hospital. In nearly all such patients it has been continued for the first six

months, after which the decision regarding its further use is made in the light of progress during this interval. We always hope to achieve freedom from dependence on digitalis. However, a few patients with excellent postoperative results have noted deterioration in their exercise tolerance and return of nocturnal respiratory distress after discontinuation of the drug, thus requiring its reinstitution. Others have developed atrial fibrillation following premature withdrawal of digitalis, likewise requiring its restoration.

Patients known to have had paroxysms of atrial fibrillation either preoperatively or in the early postoperative period are continued on a maintenance dose of quinidine for the first one to three months. The occasional late postoperative attacks of fibrillation should be treated similarly to those described for the early postoperative period.

LATE POSTOPERATIVE COMPLICATIONS

Certain complications arise with sufficient frequency in patients who have left the hospital to require discussion. Probably the commonest of these is pain in the incision, an aggravating and sometimes disabling symptom, which is well known to thoracic surgeons and which is not confined to this group of patients. The pain usually is described as a dull ache, and it may be distributed along the entire length of the operative wound or confined to any segment of it. Local infiltration with procaine sometimes is temporarily helpful, but simple analgesics have not been especially beneficial. Occasionally the entire left side of the chest may be so tender that the patient is unable to lie on it. Pain and tenderness ordinarily do not persist for longer than two or three months in patients who leave the hospital with these symptoms. Reassurance that they will disappear is more helpful than any other measure.

Reactivation of rheumatic fever has not been a problem in our series (Fig. 7). Therefore, adrenocorticotropic hormone and cortisone have not been used in postoperative treatment except in one patient. However, 10% of our patients have developed in the late postoperative period attacks of fever, chest pain, tachycardia, malaise, and sometimes heart failure. This complication has been of variable severity, but it has responded promptly and regularly to bed rest and standard cardiac management when needed. We have been impressed by the short duration of these symptoms and signs. Some writers [7] have reported a much higher incidence and have suggested that the abnormalities constitute reactivation of rheumatic fever. We are dubious of this view, and we do not consider the abnormalities to represent a syndrome peculiar to this postoperative state. We believe that multiple small pulmonary infarctions and secondary pleuritis may have an important bearing on these manifestations.

Preoperatively, patients are given an explanation of the pathology of mitral stenosis and the proposed operation. The beneficial effects of a successful operation are explained to them, but they are told frankly that the surgery is to a great extent palliative and that they will in all likelihood still have some degree of mitral stenosis after operation. Despite frequently strikingly good results we believe that this approach is sound, because many of our patients have arrived at the hospital with the concept that this type of surgery is curative and will leave them with a normal heart. We believe that it is better psychologically to prepare patients for an agreeable surprise than for an acute disappointment.

SUMMARY AND CONCLUSIONS

We have discussed the medical management of patients with rheumatic mitral stenosis in a university hospital before, during, and after mitral valvuloplasty, on the basis of experience of 95 cardiotomies with an operative mortality rate of only 4.3%.

Preoperatively congestive heart failure is controlled, and the presence of rheumatic activity or infection is excluded.

During the operation cardiac mechanism is monitored electrocardiographically and left atrial pressure pulse waves are recorded.

In the immediate postoperative period patients are watched carefully for evidence of failure of expansion of the left lung, myocardial decompensation, cardiac rhythm disturbance, and arterial embolism.

At the time of discharge from the hospital patients are given specific instructions in regard to diet, activity, and medication. The referring physicians are requested to send them back one or two months later for progress examination.

Except for incisional pain, the only troublesome last postoperative complication has been a 10% incidence of a brief, febrile intrathoracic disease process characterized by chest pain, tachycardia, malaise, and sometimes congestive heart failure. We believe this to be nonrheumatic and suggest that multiple small pulmonary infarcts and secondary pleuritis may be important factors.

Mrs. Naomi Schedl designed and drew the illustrations. Dr. Lewis E. January has given valuable advice regarding drug therapy.

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A METHOD FOR MEASURING VENOUS TONE IN DIGITAL VEINS OF INTACT MAN

Evidence for Increased Digital Venous Tone in Congestive Heart Failure

G. E. BURCH, M.D.
NEW ORLEANS

IT HAS been suggested that the tone of the veins is increased in chronic congestive heart failure,* but, because the evidence has been indirect and unconvincing, the concept has not been fully accepted.† Some of the data reported ‡ may be interpreted to support an increase in venous tone. Because the neck veins are distended in patients suffering with congestive heart failure, the blood volume is considered by many to be increased and venous tone to be decreased. That this is not necessarily true has been indicated by previous studies,§ as well as by the observation that blood volume may be only slightly to moderately increased, if at all, in congestive heart failure.‖ Thus, it is desirable to study venous tone in congestive heart failure further.

A venous occlusive pneumoplethysmographic method has recently been developed in this laboratory that permits simultaneous measurements of the continuous curves of the time courses of the volume, rate, and acceleration in rate of inflow, outflow, and difference between inflow and outflow for the intact finger tip of man.¶ This method lends itself to a study of aspects of the behavior of the veins in the intact digit of normal man as well as subjects with chronic congestive heart failure. Data presented in this report are compatible with an increase in tone in the venous, as well as arterial, side of the digital vascular bed in subjects with severe chronic right and left ventricular congestive heart failure.

Venous tone is defined as the tendency of the vein to resist distention. This resistance is due in part to a state of contraction or tension offered by the smooth muscle in the wall of the vein. Whenever there is a tendency for the vein to be distended,

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From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans.

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* References 1 and 2.

† References 3-6.

‡ References 3 and 4.

§ References 7 and 8.

‖ References 7 and 9-13.

¶ References 14 and 15.

the smooth muscle and other structures and substances of the wall offer countertension, thereby increasing venous tone. Thus, venous pressure can, within limits, be considered an index of venous tone.

MATERIALS AND METHODS

Eighteen subjects were studied, 12 women and 6 men, ranging in age from 33 to 70 years (mean, 51 years). All were bedridden patients with advanced chronic right and left ventricular congestive heart failure (Functional Group IV, classification of the New York Heart Association) who exhibited classic manifestations of severe failure, including greatly distended neck veins, high venous pressure, diffuse edema, orthopnea, and cardiac asthma. In all patients the state of failure was becoming worse, certainly not improving, except in one instance, which

TABLE 1.—*Changes in Venous Pressure Produced by Hexamethonium With and Without Pressure over the Hepatic Region of the Abdomen*

	Before Hexamethonium (C_6)				After Hexamethonium (C_6)			
Subject No.	B.P., Mm. Hg	Pulse Rate/Min.	V.P., Mm. H_2O	V.P. with Hepatic Pressure, Mm. H_2O	B.P., Mm. Hg.	Pulse Rate/Min.	V.P., Mm. H_2O	V.P. with Hepatic Pressure, Mm. H_2O
1	140/100	120	438	600+	92/72	116	280	400
2	146/114	76	316	436	116/84	68	223	318
3	144/90	100	278	358	125/80	88	240	280
4	110/70	65	356	427	78/56	80	280	370
5	110/78	80	263	323	80/50	72	135	220
6	110/80	100	390	490	76/56	108	290	390
7	178/96	80	227	397	128/74	76	202	322
8	110/60	64	169	269	78/38	60	144	169
9	100/56	68	315	480	80/36	68	250	320
10	160/100	68	388	498	124/74	76	223	333
11	186/46	96	402	552+	130/50	92	232	347
12	190/100	112	325	435	142/80	92	210	295
13	140/98	84	294	370	.....	..	...	...
14	192/94	84	348	458	172/84	76	270	440
15	200/108	80	389	459	156/86	68	295	355
16	154/110	88	300	510	100/68	88	200	370
17	156/96	84	425	550+	144/80	84	310	500
Mean	149/88	86	331	447	114/67	82	236	339
Extremes	.....	64-120	169-438	269-600+	.....	60-116	135-310	169-500
Systolic	100-200	..	...	...	76-172	..	...	...
Diastolic	46-114	..	...	...	36-86	..	...	...

is discussed separately. The etiology of the heart disease was as follows: essential benign hypertension, eight subjects; rheumatic fever with mitral stenosis, four subjects; arteriosclerosis, four subjects; syphilis with aortic insufficiency, one subject; anemia, one subject.

While the subjects rested in a hospital-type bed in an observation room with a comfortable atmosphere (temperature, 76 F.; relative humidity, 59%), plethysmographic cups # were placed on the tips of the right index (2RF) and right middle (3RF) fingers. The pneumatic cuff for occlusion of venous return from the finger tip was placed, as previously described, against the plethysmographic cup on the second right finger tip.* An electromagnetic pickup responsible for the signal which activated the electronically controlled solenoid valve guarding the occluding cuff was applied to the third left finger tip (3LF). The time courses of the rate and volume of blood flow into and out of the second right finger tip were then simultaneously determined, as described in detail elsewhere.[15] Corrections for size of the finger tips were made to reduce all values to the unit of 5 cc. of part.† Change in total volume of 2RF associated with admin-

References 15 and 16.

* References 14 and 15.

† References 15 and 16.

istration of hexamethonium was measured in five subjects. The temperature of the air in the plethysmographic cup was recorded by means of thermocouples sensitive to 0.1 C. change in order to correct, if necessary, for changes in volume within the cup due to thermal influences.

After rates and volumes of blood flow were recorded with the subject at rest, his venous pressure was determined [17] in the left median basilic vein prior to and following manual application of pressure over the hepatic area (hepatojugular reflux). While the arterial blood pressure was being recorded sphygmomanometrically in the right or left arm and the venous pressure in the left median basilic vein, hexamethonium was slowly injected intravenously until the venous pressure had decreased decidedly and/or the arterial blood pressure had declined to a level considered safe (consult Table 1 for levels attained). The minimal dose of hexamethonium was 5.0 mg., and the maximal was 25 mg., the total dose being injected within 2 to 14 (mean, 8) minutes. After the arterial blood pressure and venous pressure had reached a stable level, pressure was again applied manually over the hepatic area, and the change in venous pressure was noted. The venous pressure was also recorded when pressure was applied over other abdominal areas, as well as during periods of clenching of the left fist

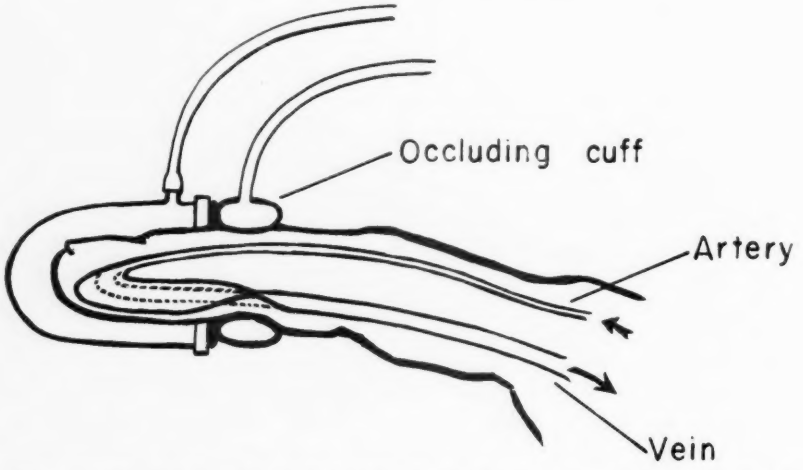

Fig. 1.—Diagram of a finger tip in a plethysmographic cup, showing accumulation of blood in the "venous" reservoir (dotted line) from arterial inflow when the occluding cuff is inflated.

by the subject. Finally, during the course of full effects of the hexamethonium, the rates and volumes of blood flow into and out of the right index finger tip were again simultaneously recorded.

THEORETIC CONSIDERATIONS

For adequate understanding of the pneumoplethysmographic method employed to measure the state of tone in the digital veins, the reader is referred to a previous publication.[15] It is also desirable to review briefly the venous occlusive pneumoplethysmographic method used in these studies.

In this method the finger tip was enclosed within the plethysmographic cup (Fig. 1), and changes in volume of the finger tip with time were recorded photographically. For recording the rate of inflow of blood, venous outflow was suddenly obstructed by inflation of the occluding cuff to 60 mm. Hg pressure. The inflowing blood accumulated in the "venous reservoirs," [15] or capacity vessels, of the finger tip and produced an increase in volume of the tip of the finger, which was recorded.

By a method previously described,‡ simultaneous time courses of rates and volumes of inflow and outflow were obtained. It was postulated in these studies that when venous tone is high, i. e., when the venous system is "tight," the venous reservoir should accommodate only small quantities of blood before the pressure in the veins distal to the occluding cuff would exceed the pressure in the occluding cuff, causing blood to leak past the occluding cuff. Consequently, the plethysmographic trace should reach a plateau early, resulting in a rapid decline to a zero "recorded" rate

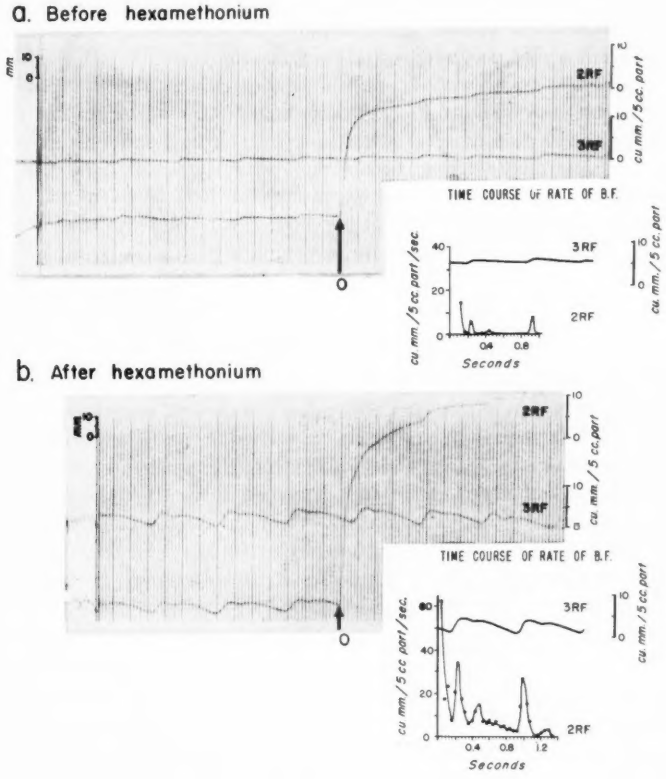

Fig. 2.—The recorded plethysmograms and curves of the time courses of the rates of inflow of blood (inserts) (*a*) before and (*b*) after intravenous injection of hexamethonium in a representative patient with advanced chronic congestive heart failure. The "recorded" rate of flow was low and reached a zero value much more rapidly before the administration of hexamethonium than afterwards. The label 2RF indicates the second right finger tip and 3RF, the third or middle right finger tip in this and all illustrations to follow. The volume pulse waves for 3RF are shown at the top of each insert, with the ordinate at the right. The time course of the rate of blood inflow for 2RF is shown at the bottom of the insert, with its ordinate at the left. The 10 mm. scale on the left is included to illustrate reduction in actual size associated with reproduction. The curves in the inserts were plotted from the pulse cycles immediately following inflation of the cuff which occluded venous return at arrow O. Details of analysis of the records were described elsewhere.[15] B. F. indicates blood flow.

‡ References 14 and 15.

of blood flow in the finger tip (Fig. 2*a*).[15] This recorded rapid decline in rate of inflow also reflected a rapid decline in arteriovenous pressure gradient in the part of the digit isolated for study.

On the other hand, when venous tone is low or reduced, as, for example, after intravenous injection of a sympathetic nerve ganglionic blocking agent, such as hexamethonium (Table 1), the recorded rate of blood flow should reach zero more slowly following occlusion of venous flow, since the venous reservoirs would be loosened and, being more distensible, would therefore be able to accommodate a larger volume of inflowing blood following obstruction to venous outflow (Fig. 2*b*). Furthermore, with lower venous tone and more distensible veins, the arteriovenous pressure gradient would decline less rapidly following obstruction to digital venous outflow. This would be associated with less rapid decline in rate of inflow recorded by the plethysmogram (Figure 2*b*). These theoretic plethysmographic considerations were applied to the finger tip of subjects with chronic congestive heart failure in an effort to determine whether or not the venous system is tight, i. e., whether the tone in the veins of the finger tip is increased. Furthermore, applications of these concepts to the method of venous occlusive plethysmography also test its usefulness in this type of study of the veins of any part similarly isolated.

RESULTS

Tone of the Veins of the Finger Tip

A. Volume-Time Curves of the Plethysmogram.—Figure 2*a* shows a typical recorded plethysmogram of a subject with advanced chronic congestive heart failure. The volume curve approached, and actually reached, a zero slope early during the interval of the first pulse cycle following obstruction to venous outflow from the finger tip in all the subjects (except one, described in the discussion) with congestive failure at rest and prior to administration of hexamethonium. This horizontal course in the original complete plethysmogram (Fig. 2*a*) developed quickly, even though the volume change immediately following obstruction to the veins was relatively small. However, this does not establish absence of flow during the later portion of the pulse cycle but rather indicates a rapid increase in pressure in the veins distal to the occluding cuff to a level exceeding the pressure within the occluding cuff, as postulated previously, causing blood to leak past the occluding cuff. Although the arteriovenous pressure gradient in the finger tip must have declined, it probably did not reach a zero value nor did inflow of blood cease, because pressure in the occluding cuff was less than the diastolic pressure on the arterial side of the circulation. That leakage of blood past the occluding cuff developed and that inflow was not actually zero is supported further by the fact that the volume pulse wave for the third right finger tip (3RF), recorded simultaneously for the same pulse cycle, and the volume pulse wave for the right index finger tip (2RF) just prior to obstruction to venous outflow, showed a change in volume of the finger tip (a descent). Thus, blood must have been flowing out of the finger tip at this time, because the volume pulse wave represents the difference between volume inflow and outflow, especially since the pressure in the occluding cuff was less than diastolic arterial blood pressure. Therefore, the volume pulse wave indicated a greater flow out of than into the finger tip (Fig. 2*a*) when the inflow trace indicated no flow into or out of the finger tip. Furthermore, all volume pulse waves for 2RF showed a volume

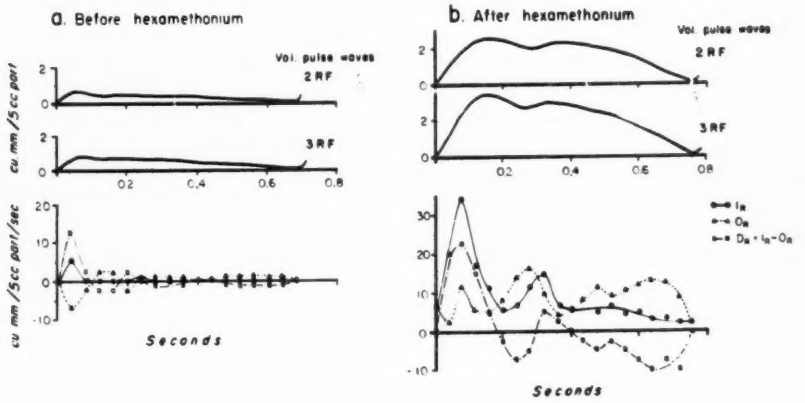

Fig. 3.—The "recorded" simultaneous curves of the time courses of the rate of inflow (I_R), rate of outflow (O_R), and difference (D_R) between I_R and O_R in 2RF of the patient with chronic congestive heart failure whose plethysmograms are shown in Figure 2.

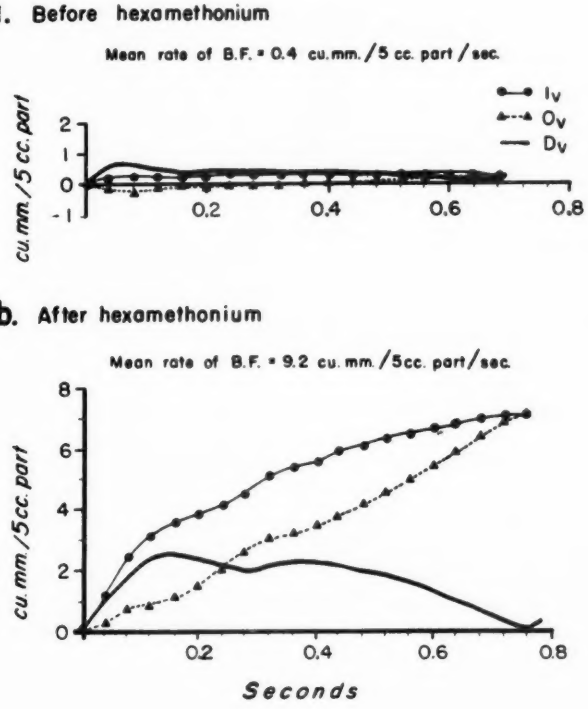

Fig. 4.—The "recorded" simultaneous curve of the time courses of the volume of inflow (I_V), volume of outflow (O_V), and difference (D_V) between I_V and O_V in 2RF of the patient with advanced chronic congestive heart failure whose curves are shown in Figures 2 and 3. The effects of intravenous administration of hexamethonium are evident. Consult the text for details.

change throughout the pulse cycle (Fig. 3*a*), indicating that blood was flowing into the finger tip and that flow was not actually "zero," as recorded. It may be argued that inflow was zero while outflow continued to occur. It is unlikely, however, that the many adjustments necessary for outflow to exist in the absence of any inflow would develop simultaneously in the vessels and in the hemodynamic state in the intact finger tip. Furthermore, by proper recording of blood flow [15] to avoid error due to leakage, inflow and outflow were recorded throughout the pulse cycle (Fig. 10). Therefore, the recorded flow of "zero" must reflect "tight" veins and high venous tone.

That venous tone was increased is further supported by the response obtained and recorded by the plethysmogram to intravenous injection of hexamethonium (Fig. 2*b*). After administration of the drug, the rate with which the "zero" recorded flow or horizontal course of the volume-time trace developed for 2RF following venous occlusion was strikingly reduced in all subjects studied. At the same time, the rate of inflow of blood was greater, despite a decline in the arterial blood pres-

TABLE 2.—*Influence of Hexamethonium (C_6) on Digital Blood Flow in Congestive Heart Failure**

	Rate of Blood Flow, Cu. Mm./5 Cc. Part/Sec.					Total Volume Inflow, Cu. Mm./5 Cc. Part
	Maximal Inflow	Minimal Inflow	Mean Inflow	Maximal Outflow	Minimal Outflow	
A. Before Hexamethonium						
Mean	33.0	0.6	7.6	19.9	1.0	5.4
Extremes	5.5-51.0	0.0-2.0	0.4-17.1	2.5-36.0	0.0-3.5	0.3-13.0
B. After Hexamethonium						
Mean	52.9	4.1	14.5	30.9	2.6	11.5
Extremes	34.0-70.0	1.0-10.0	9.1-23.0	16.5-38.0	0.0-7.5	6.9-23.9
C. Change due to Hexamethonium						
Mean †	19.9 (145.0% †)	3.5	6.9 (397.0% †)	11.0 (134.0% †)	1.6	6.1 (419.0% †)
Extremes	7.0-30.0 (18.4-518.0%)	1.0-8.0	3.3-11.5 (34.5-2175.0%)	1.0-22.0 (2.8-560.0%)	0.0-7.5	1.7-10.9 (31.5-2200.0%)

* Rates of digital flow before and after hexamethonium for seven patients with congestive failure who were progressively becoming worse were used in calculating these values. Values for the other 10 subjects were not included, since the observations were designed to measure primarily changes in total volume of the digit following administration of the drug.

† Obtained by averaging the individual changes.

sure. The decline in arterial blood pressure favored a rapid decrease in the arteriovenous pressure difference toward zero, and the greater volume of inflow would have tended to produce more rapid filling of the venous reservoirs. These observations indicate a "loosening" and decrease in tone of the venous reservoirs of the finger tip from a tight venous system, or a system of high tone, to one of low tone, in response to the sympathetic ganglionic blocking agent. Furthermore, the total volume of the finger tip increased (extremes, 8 to 64 cu. mm. per 5 cc. finger tip; mean, 38 cu. mm. per 5 cc. finger tip) after administration of hexamethonium in the five subjects in whom it could be recorded. For this to have occurred while systemic venous pressure was declining, inflow to the finger tip increasing, and the "venous reservoir" of the finger tip loosening, the tone of the smooth muscle in the walls of the veins must have decreased under the influence of hexamethonium.

B. Time Courses of Rate of Inflow, Rate of Outflow, and Difference Between Rates of Inflow and Outflow.—The simultaneous curves of the rates of inflow and outflow and difference between the rates of inflow and of outflow as determined

for the subject with advanced chronic congestive heart failure before (Fig. 3*a*) and after (Fig. 3*b*) injection of hexamethonium were obtained from the plethysmograms shown in Figure 2*a* and *b*. The rate of inflow prior to administration of the drug declined to a "zero" recorded level within the interval of a pulse cycle following occlusion of venous return, as would be expected from the original recorded plethysmogram. That this recorded zero rate of flow was erroneous and was due to leakage past the occluding cuff is supported by the curve of the rate of outflow, which has a positive value. This statement is true because the volume pulse wave of 3RF recorded simultaneously with the flow recorded for 2RF, as well as the volume pulse wave of 2RF recorded just prior to venous occlusion, manifested a volume change throughout the pulse cycle. When the tone of the venous reservoir was reduced by hexamethonium, the recorded rate of inflow did not decline to zero

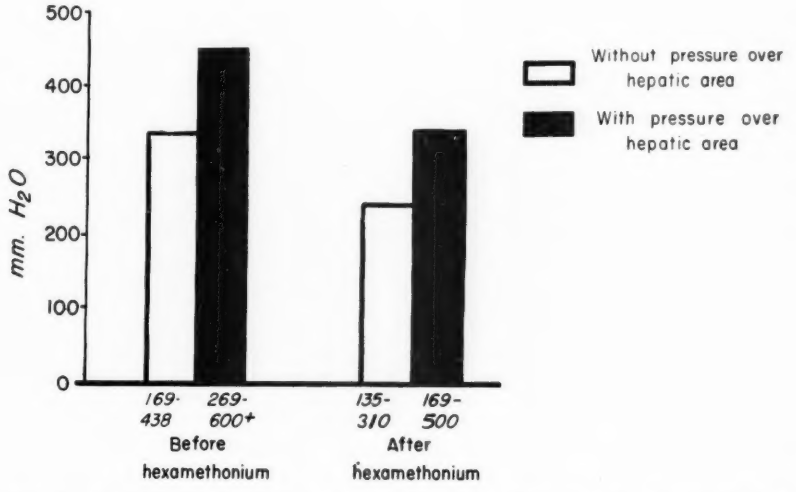

Fig. 5.—Venous pressure recorded in the left median basilic vein in the left antecubital fossa at heart level before and after the intravenous administration of the hexamethonium to the subjects with advanced chronic congestive heart failure.

during the interval of the first pulse cycle following occlusion of venous return (Figs. 2*b* and 3*b*).

C. Time Courses of Volume of Inflow, Volume of Outflow, and Difference Between Volumes of Inflow and Outflow.—Figure 4*a* shows the recorded volume of inflow to decline to "zero" during the first pulse cycle following obstruction to venous return. The total recorded volume of inflow is also found to be relatively small. At the same time, the recorded volume of outflow did not necessarily decrease to zero. As for the curve of the rate of inflow, the decline in recorded volume of inflow was due to the tight venous reservoirs, which caused them to overfill rapidly. That the high venous tone associated with the congestive heart failure was reduced by hexamethonium is evidenced by failure of the recorded volume inflow to reach "zero" during the first pulse cycle following venous obstruction despite a considerable increase in the volume of inflow (Fig. 4*b*).

The small magnitude of the volume pulse wave during congestive heart failure (Figs. 2*a* and 3*a*) was probably due not only to increased arteriolar and arterial tone, with narrowing of the lumina of the arterioles and arteries and consequent reduced digital blood flow, but also to the increased tone and possible narrowing of the veins, arteriovenous anastomotic vessels, and probably capillaries, which increased fric-

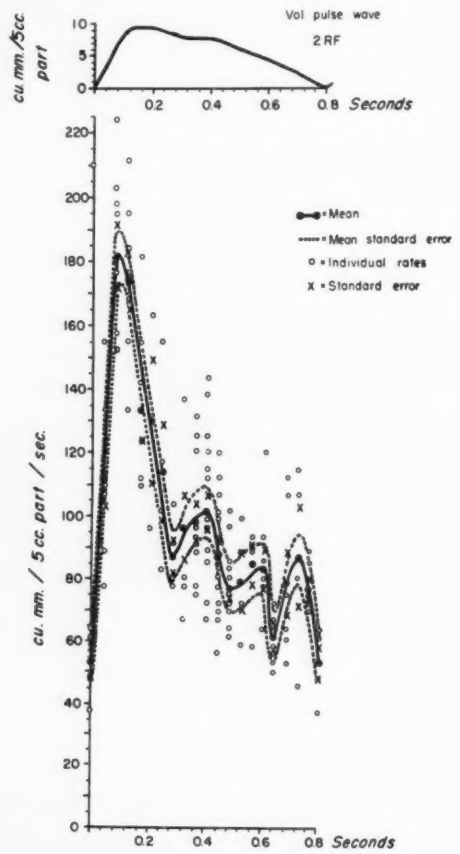

Fig. 6.—The time course curve of the mean rate of inflow in 2RF and curves of the mean standard error of the mean inflow values of a normal subject resting quietly in bed in a comfortable environmental atmosphere with the finger at heart level These curves were constructed from 152 different values from 45 pulse cycles in which the rates of inflow were measured. In almost all instances the values of the rates were obtained at each 0.04 second for an interval of 0.08 to 0.24 second following occlusion of venous return, to avoid or reduce errors due to leakage, hemodynamic effects, or venous overdistensibility. Only occasionally were the intervals as early as 0.04 and as late as 0.32 second following occlusion to venous outflow employed. The mean volume pulse wave of 2RF is shown at the top, placed in time with the rate curve.

tional resistance and also decreased pulsatile distensibility with each heart beat. Administration of hexamethonium increased the magnitude of the volume of the pulse wave because of a decrease in the previously high vascular tone, including

venous tone, with resultant greater blood flow (Table 2; Figs. *2b*, *3b*, and *4b*). That the veins participated in the volume pulsations in the finger tip is evidenced by the fluctuations in magnitude of the time course of the rate and volume of outflow (Figs. 6 through 11).

Tone of the General Systemic Veins of the Body

The venous pressure in the left median basilic vein, recorded directly by the phlebomanometer,[16] was elevated (mean, 331 mm. H_2O; extremes, 169 and 438 mm.

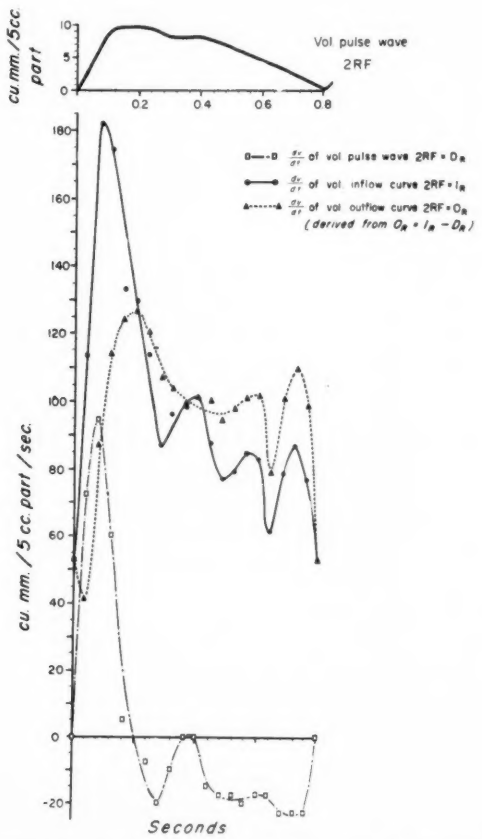

Fig. 7.—The simultaneous mean time courses of the rate of inflow (I_R), rate of outflow (O_R), and difference (D_R) between I_R and O_R, obtained from the mean curves shown in Figure 6 for the resting normal subject.

H_2O) (Table 1; Fig. 5). With the subjects sitting erect, the external jugular veins were also distended bilaterally to the mandibles. When pressure was exerted over the hepatic region, the pressure in the left median basilic vein increased to a mean of 447 mm. H_2O (extremes, 269 and 600+ mm. H_2O) (Table 1; Fig. 5). After intravenous administration of hexamethonium, the venous pressure in the left

median basilic vein manifested a mean value of 236 mm. H_2O but rose to only 339 mm. H_2O with pressure over the hepatic region (Table 1; Fig. 5). The rise in venous pressure in the patient with congestive heart failure in association with pressure over the hepatic area is further evidence of a tight venous system, due in large part to high venous tone in the systemic veins in chronic congestive heart failure.[8] The tone of the veins was decreased by the hexamethonium, and the pressure upon the hepatic region of this "loosened" venous system resulted in less absolute rise in

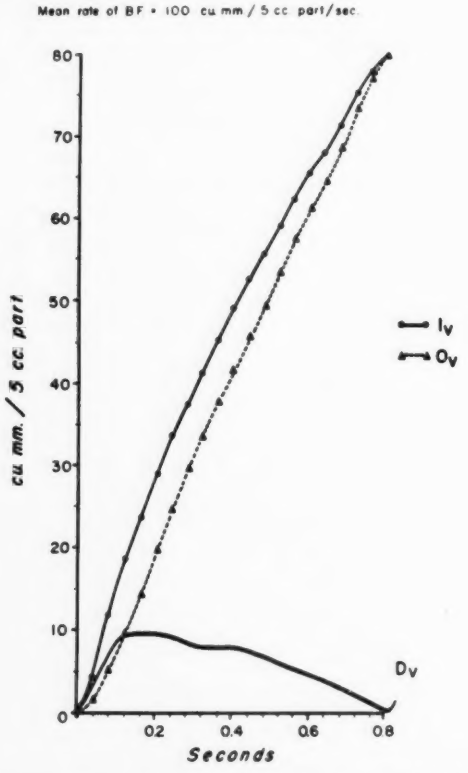

Fig. 8.—The simultaneous mean time courses of the volume of inflow (I_V), volume of outflow (O_V), and difference (D_V) between I_V and O_V for the normal resting subject whose rate curves are shown in Figures 6 and 7. D_V is the same as the mean volume pulse wave.

venous pressure. Associated with the decline in pressure recorded in the left median basilic vein was a diminution in pressure in the external jugular veins, as manifested by their collapse and reduction in turgidity. Thus, the tone of the larger systemic veins was increased along with the tone of the veins of the finger tip in the subjects with congestive heart failure. The collapse of the veins of the neck indicated a shift of blood elsewhere in the vascular system. The shifting of blood volume must have occurred, as evidenced by alternation in static or dynamic forces within the vascular system.

Rate of Digital Blood Flow

Although no attempt was made to study the rate and volume of digital blood flow in detail, the rate of digital (2RF) blood flow was considerably lower in the patients with chronic congestive heart failure than in the normal subjects. This is evident upon comparison of the representative plethysmogram and the curves of rate and volume for a normal subject (Figs. 6 through 8) § with those for a subject

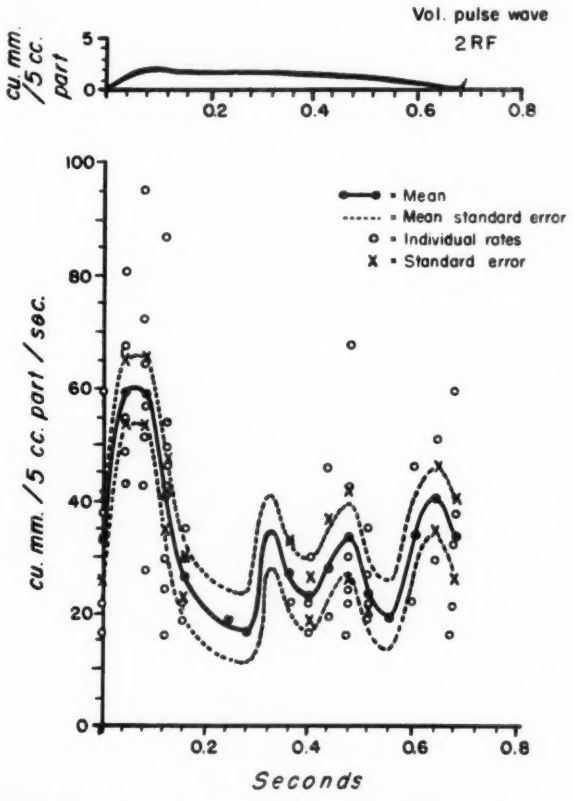

Fig. 9.—The time course curve of the mean rate of inflow in 2RF and curves of the mean standard error of the mean inflow values of a representative subject with severe chronic congestive heart failure resting quietly in bed in a comfortable environment with the finger at heart level. These curves were constructed from 60 different rate values within 30 pulse cycles in which the rate of inflow was measured. The values of the rates were obtained in almost all instances for the interval from 0.08 to 0.16 second intervals following occlusion of venous return, to avoid or reduce errors due to leakage, hemodynamic influences, or venous overdistensibility. Only occasionally were intervals as early as 0.04 or as late as 0.28 second following obstruction to venous outflow employed. The mean volume pulse wave for 2RF at the top of the illustration was placed in time with the rate curve.

with chronic congestive heart failure (Figs. 9 through 11). These mean time courses of rates and volumes of flow for a single pulse cycle for a normal resting subject were

§ References 14 and 15.

plotted from 152 measurements of flow for approximately 45 separate pulse cycles. Only the early portion of the pulse cycle was measured, to avoid errors due to overfilling of the venous reservoirs, usually from 0.08 to 0.24 second after venous obstruction; occasionally, the interval used began as early as 0.04 second or ended as late as 0.32 second. Venous occlusion was applied at 10 different time phases of the pulse cycle, in order to attain maximal accuracy in construction of the curves of flow (Figs. 6 through 8). This method of recording blood flow has been described in detail elsewhere.[15]

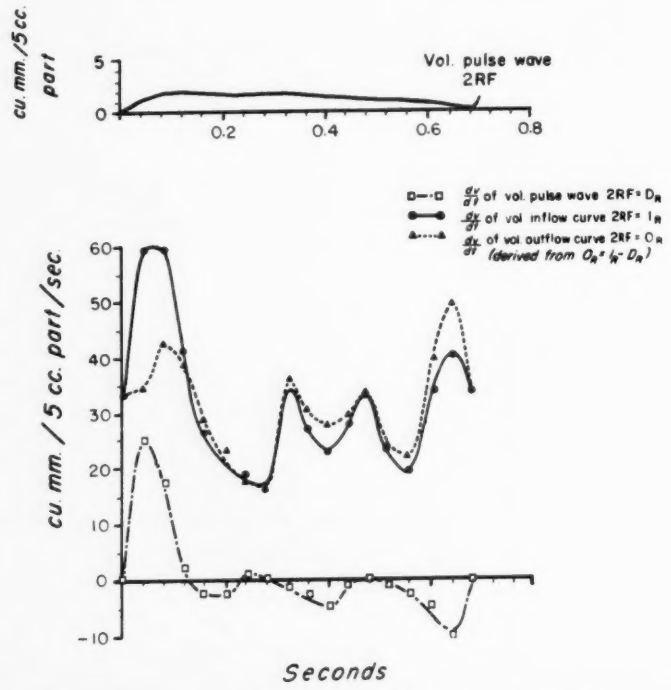

Fig. 10.—The simultaneous mean time courses of the rate of inflow (I_R), rate of outflow (O_R), and difference (D_R) between I_R and O_R obtained from the mean inflow curve and mean volume pulse curve shown in Figure 9 for the patient with congestive heart failure. Comparisons between these curves and those in Figure 7 will disclose the differences between the normal subject and the patient with heart failure.

Curves of the time course of blood flow for the subject with chronic congestive heart failure were also obtained under the same environmental and experimental conditions as for the normal subject. Sixty measurements of flow from 30 pulse cycles were employed to plot the mean curves for the representative patient with chronic congestive heart failure. That portion of the pulse cycle from the first 0.08 to 0.16 second following venous occlusion was employed for the measurements of flow; only occasionally were intervals beginning as early as 0.04 or ending as late as 0.28 second employed. Venous occlusion was applied at 10 different time phases during the pulse cycle, to yield values of flow which would permit the mean curves

(Figs. 9 through 11) || to be as free as possible from errors due to rapid overfilling of the venous reservoirs. This was particularly important in the presence of congestive failure, because of the tight venous reservoir and high digital venous tone demonstrated earlier in this study. A study comparing these curves of flow for the normal subject with those for the patient with congestive heart failure reveals a much lower digital flow in the presence of failure. Although measurements were obtained in detail for only one abnormal representative subject, observations were consistent for all subjects. The rate and volume of blood flow definitely increased after administration of hexamethonium in the subjects with congestive heart failure; the influence of the drug was not studied in normal subjects.

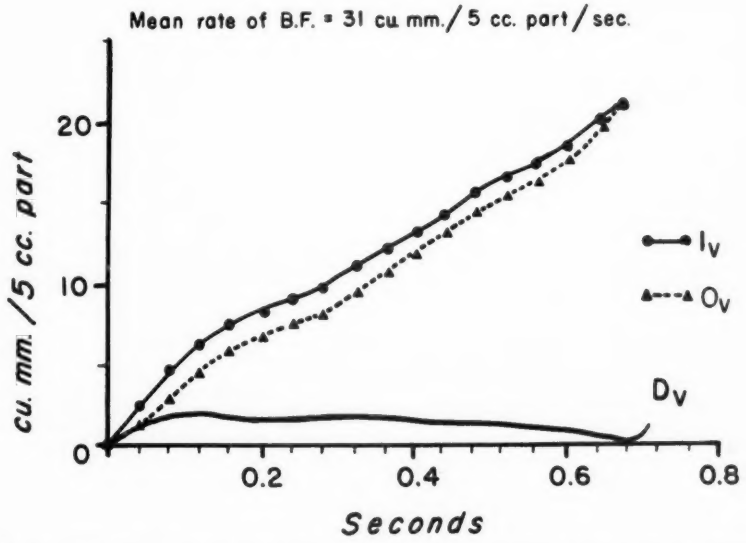

Fig. 11.—The simultaneous mean time courses of the volume of inflow (I_V), volume of outflow (O_V), and difference (D_V) between I_V and O_V obtained from the curves in Figures 9 and 10 for the subject with congestive failure. Comparisons between these curves and those in Figure 8 will reveal the differences between the normal subject and the patient with congestive failure.

That the low rate of digital blood flow in the patients with congestive failure was due largely to arteriolar vasoconstriction in the finger tips and not merely to decreased cardiac output associated with the failure seems feasible because the differences between the rates and volumes of digital blood flow for the normal subjects and for the patients with failure were greater than would be expected from differences in cardiac output alone. The increase in volume of the pulse waves and in rate and volume of blood flow in the digit (2RF) following administration of hexamethonium demonstrates that arteriolar dilatation was produced by the drug. As indicated earlier in this report, the tone of the venous side of the digital vessels was also reduced by hexamethonium.

|| References 8, 13, and 14.

COMMENT

These plethysmographic studies indicate a tight venous system in the finger tip, due in large part to an increase in digital venous tone, in advanced chronic congestive heart failure. The following evidence in support of this conclusion was obtained in these experiments:

1. With the patients at rest in a comfortable environment and the finger tip at heart level:
   A. The venous reservoir of the finger tip was tight and therefore able to accommodate only a small volume of inflowing blood proximal to the cuff occluding venous outflow before the pressure in the venous reservoir became greater than that in the occluding cuff, causing leakage past the cuff.
   B. The volume of the pulse wave was small, indicating increased arteriolar tone in association with the tight vascular system beyond the arterioles.
   C. Venous pressure in the systemic veins was high.
   D. Pressure upon the hepatic area resulted in a much further increase in systemic venous pressure, a response which is to be expected when pressure is exerted upon a tight closed vascular system.
   E. The rates and volumes of digital inflow and outflow were low in comparison with those for normal subjects.
2. The following peripheral vascular responses were obtained in the subjects with advanced failure following intravenous administration of hexamethonium:
   A. The digital venous reservoir loosened, as evidenced by its ability to accommodate a much larger quantity of inflowing blood before pressure within the venous reservoir of the finger tip increased to exceed the pressure in the occluding cuff, with resultant leakage past the cuff.
   B. The volume of the pulse waves increased greatly despite a decline in arterial blood pressure, indicating a decrease in arteriolar tone.
   C. Venous pressure in the systemic veins decreased, indicating a loosening of the venous system generally.
   D. Pressure over the hepatic area resulted in a rise in venous pressure to a lower level than that before administration of hexamethonium. This response would be expected when pressure is exerted upon a relatively loose closed vascular system.
   E. The over-all volume of the finger tip increased after administration of hexamethonium, in association with a decline in venous pressure and other reactions. Therefore, this must indicate relaxation of the previously tense smooth muscle in the digital veins.
   F. The rates and volumes of digital inflow and outflow increased greatly in spite of a decrease in arterial blood pressure, a response compatible with a decrease in arteriolar tone and vasodilatation in the vessels distal to the arterioles. The foregoing changes cannot be explained merely on the basis of changes in cardiac output and in the arterial and arteriolar systems.

Because of the high tone, the absolute values of the curves of inflow and outflow shown in Figures 2 through 4 were accurate only for the early portions of the first pulse cycle, during which venous obstruction was produced, before blood had leaked past the venous occluding cuff. Errors in measurement, due to rapid overfilling of digital venous reservoirs of the patients with congestive failure and to a progressive decline in the arteriovenous pressure gradient, gradually increased as the pulse cycle progressed, so that probably only the values of about the first 25% of the pulse cycle were correct. A comparative study of the curves shown in Figures 2 through 4 and 9 through 11 reveals that when the mean curves were carefully obtained, so as to avoid errors produced by overfilling of the veins, the curves of rate and volume were

adequate. It is evident that these traces (Figures 9 through 11) show blood to flow into and out of the finger throughout the pulse cycle in the subjects with advanced congestive failure.

Even though errors due to leakage existed, the data reveal a lower rate and volume of digital blood flow in the subject with congestive heart failure than in the normal subject. This is clearly demonstrated even for the initial portions of the pulse cycles measured in Fig. 2*a* and *b*, before errors due to high venous tone had had an opportunity to become manifest, when these curves are compared with those for the normal subject shown in Figs. 7 and 8. Studies on a much larger series of subjects under many circumstances of therapy, state of failure, etiologic disease states of the heart, and other circumstances are needed. The present experiments did not permit, nor were they designed for, a detailed study of simultaneously recorded curves of rate and volume of inflow and outflow, although several hundred rates of digital blood flow were recorded for the subjects with failure.

That blood flow to the finger tip is decreased in chronic congestive heart failure is not surprising,[18] although the simultaneous curves of time courses of rate and volume of digital blood flow during a single pulse cycle have not been described previously. Careful inspection of these curves reveals interesting temporal qualitative and quantitative details concerning digital blood flow and the circulation in the intact finger, as well as definite differences from the curves of normal subjects. The characteristic cold, clammy skin and acral portions of the body of patients with congestive failure are compatible with reduced blood flow. Reduction in the circulation to the digits may be related to a physiologic effort to shift the limited supply of ejected blood to the more vital organs of the body, an expression of the previously described physiologic phenomenon of hemometakinesia.[19]

The results were the same in all subjects studied except one in whom pressure in the left median basilic vein was 320 mm. H_2O and in whom manual application of pressure over the hepatic area failed to produce an elevation in venous pressure. Furthermore, after administration of hexamethonium his venous pressure was not reduced. Manual application of pressure over the hepatic area at this time produced a decrease in venous pressure. Digital blood flow after administration of hexamethonium did not change from a previously relatively high rate of flow. The total volume of the finger tip declined after hexamethonium. This failure of venous pressure to change in response to pressure over the hepatic area in a patient with congestive heart failure and high venous pressure is most unusual and may be attributable to special physiologic circumstances of his state of heart failure, unknown complicating facts, existing physiologic states, or therapy. It may be due to the fact that this patient's congestive failure was definitely improving, whereas in the other subjects studied the failure was becoming worse and surely not improving. It might be expected that as compensation begins venous tone becomes reduced, and these physiologic responses may be quantitatively related to each other. The state of the failure, therefore, must be considered when venous tone and the vascular system are being evaluated.

The method described for study of the tone of the venous side of the digital vessels should be applicable to other portions of the body, even if they are large, provided the apparatus is modified to meet the requirements of the part. The method is relatively simple and can, moreover, be applied to intact man, permitting simul-

taneous study of the venous as well as the arterial side of the vascular system. The influence of drugs and other agents upon the physiologic states of the arterial and venous sides of the circulation simultaneously, including tone of the venous side, can also be studied by this method.

The mechanisms or physiologic reasons for the increase in tone of the veins of the finger tip and systemic veins in congestive heart failure remain unknown. The increase in tone is most probably related in large part to a generalized increase in sympathetic venoconstrictor activity.[21] The role played by the increase in venous tone in the clinical manifestations and physiologic adjustments in congestive heart failure also remain unknown, although it must contribute significantly to them. The clinical improvement following intravenous administration of hexamethonium in the patients suffering from cardiac asthma and other evidences of respiratory distress was dramatic at times during the experiments. All patients were improved by the drug, the degree of improvement tending to vary directly with the decline in venous pressure. Improvement was associated with decrease in dyspnea, decrease in rales and wheezes in the lungs, disappearance of cough, disappearance of gallop rhythm and pulsus alternans at times, a feeling of considerable psychic improvement with disappearance of panic and distress, and, in several instances, diuresis and ultimately compensation clinically. All patients were receiving the usual treatment for congestive heart failure before, during, and after administration of hexamethonium but were considered clinically to have severe, if not intractable, failure.

Since cardiac output, cardiac reserve, or cardiac work was not measured, it is not possible to know the causative relationship of the reduction in venous pressure and other physiologic adjustments to cardiac function and clinical improvement. Nevertheless, the decline in venous pressure and clinical improvement were directly related quantitatively during these experiments. The reduction in arterial blood pressure which followed administration of hexamethonium may have reduced the load on the heart sufficiently to account for a part of the cardiac improvement. It is possible, however, that the reduction in venous tone, including that in the pulmonary veins, was also of considerable, if not equal, importance. In fact, it would appear that reduction in pulmonary venous pressure was necessary for the almost immediate improvement in the respiratory symptoms and signs.[20]

The change in venous tone recorded in the finger tips following administration of hexamethonium was not caused directly by a change in cardiac output. However, improvement in cardiac function and output may have altered to some extent the mechanisms responsible for the decrease in venous tone. It would appear that the drug, at least in part, blocked the sympathetic impulses to the veins and to the arterioles as well, reducing their tone. Dilatation of the arterial side of the digital vascular system which followed administration of the drug could not alone have been responsible for all the changes in the plethysmograms and the rate and volume curves. In fact, dilatation of the arterioles, with an increase in the rate and volume of inflow of blood, would tend to produce alterations in these curves which would have camouflaged the pattern caused by venous tone.

Finally, careful inspection of the simultaneous curves shown in all the figures reveals many interesting and important aspects of hemodynamic states and other peripheral vascular physiologic processes related to congestive heart failure which were not discussed in this report.

SUMMARY

A digital phethysmographic method has been described for observing variations in tone of the venous side of the vascular bed of intact man. Venous tone of the finger tip of patients with advanced chronic congestive heart failure was found to be elevated.

The rates and volumes of inflow, outflow, and difference between inflow and outflow for the finger tip were reduced in the patients with chronic congestive heart failure. Simultaneously recorded curves of the time courses of rates and volumes of inflow and outflow and of the difference between the rates and volumes of inflow and outflow are illustrated, which, upon careful study, reveal many interesting physiologic aspects of digital inflow and outflow in congestive failure.

During the course of these experiments it was again observed that the systemic venous tone in all of the patients with chronic congestive heart failure was elevated considerably. It was suggested that the increase in venous tone was due in large part to a generalized increase in sympathetic venoconstrictor activity. The relationship of the elevated venous tone to the clinical manifestations of congestive heart failure has been discussed.

An accidental observation was that the intravenous administration of hexamethonium for purposes of experimentally reducing venous tone produced considerable to even dramatic improvement in the clinical symptoms and signs of advanced congestive failure; the degree of the improvement tended to be directly related to the degree of reduction in venous pressure, but the causative relationship of these two phenomena has not been determined.

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STURGE-WEBER SYNDROME (ENCEPHALOTRIGEMINAL ANGIOMATOSIS)

GERALDINE KING, M.D.
AND
GABRIEL A. SCHWARZ, M.D.
PHILADELPHIA

THE CLASSIC clinical manifestations of the Sturge-Weber syndrome include a vascular nevus of the face, a hemiplegia contralateral to the cutaneous lesion, an intracerebral calcification found roentgenographically ipsilateral to the nevus flammeus, various abnormalities of the ipsilateral eyeball, convulsive seizures, and mental retardation. This condition seems to have received more attention in the European literature. Indeed, Nussey and Miller [1] and McCoy and Voris [2] have gone so far as to suggest that the prevalence of this disorder may be greater in continental Europe. However, it would seem to us that there may well be many cases which really belong in the category of this malady but may be unrecognized because the entire clinical picture is not present.

We have had the opportunity to study five patients with the Sturge-Weber syndrome who presented signs and symptoms in combinations varying from the cardinal features mentioned above. It was felt that a presentation of these cases and a review of the many interesting problems encountered in this disease entity might draw attention to its marked clinical variability and hence stimulate further observations on this unusual condition.

HISTORICAL REVIEW

In 1879, W. Allen Sturge [3] reported "A Case of Partial Epilepsy Apparently Due to a Lesion of One of the Vasomotor Centers of the Brain." In this report, he described a 6½-year-old girl born with a cutaneous vascular nevus of the right side of her head and face and both sides of her trunk to the third and fourth dorsal vertebrae on the back and to the second costal cartilage on the front. The nevus stopped in the midline of the upper face but was bilateral on the chin and below. The nasal and oral mucous membranes and the eye on the right side were involved by the vascular anomaly. The right eye was larger, and there was involvement of the choroidal and retinal vessels. The onset of left-sided fits had occurred at the age of 6 months, at which time progressive weakness of the left extremities began. Sturge postulated that there was a focal cerebral lesion, similar to that found on the face, which was causing the convulsions. He felt that this lesion was on the sur-

From the Department of Neurology, School of Medicine, University of Pennsylvania.

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face of the brain, external to the nerve tissue. Actually, this clinical picture had been described previously by Schirmer,[4] but without any suggestion as to the relationship of the cutaneous and neural lesions.

In 1906, Cushing [5] reported three cases of facial vascular nevi with ocular and neurologic involvement. At operation two of his cases showed increased vascularity of the skull and dura mater on the side of the facial nevi. He emphasized the fact that the vascular anomalies occurred in the distribution of the trigeminal nerve—on the face, on the scalp, and even in the dura mater.

Weber in 1922 [6] reported on a patient with a right-sided hemihypotrophy, a right-sided congenital spastic hemiplegia, and widespread cutaneous vascular nevi. The vascular nevi were chiefly of the superficial, port-wine-stain type and involved the trunk only on the left on the back but on both sides on the front. There was bilateral involvement of the face, but on the left side the vascular abnormality was more deep-seated (cavernous angioma). The patient's left eye was blind and showed optic atrophy, glaucoma, and heterochromia iridis. No seizures were described for this patient. Roentgenograms of the skull revealed the left half of the brain to be more opaque than the right half.

This case was again reported on by Weber in 1928.[7] At this time well-defined left cerebral calcifications were demonstrable in the roentgenograms of the skull. They were felt to represent partially calcified leptomeninges. This explanation was made possible by Kalischer's case (1897)[8] with a necropsy report (1901)[9] of a smaller left cerebral hemisphere covered with a diffuse meningeal angioma. Also in 1928, Brushfield and Wyatt [10] described a left meningeal angioma and other cerebral defects in a patient who had had a right spastic hemiplegia. Although Wissing (1921),* Dimitri (1923),[11] and Marque (1927)[12] had previously noted intracranial calcifications roentgenographically in this condition, Weber is usually designated as the first person to have described them.

Van Bogaert [13] gave Volland [14] credit for the first histologic description of the calcium deposits in the involved cerebral cortex in such cases. Hebold (1913)[15] also noted the calcium deposition in the affected cortex. He further noted the involvement of all the derivatives of the primordial head in this condition and emphasized the fact that the vascular malformation determined the cerebral malformation.

The next significant addition to this interesting syndrome was that of Krabbe, in 1934.[16] He reported five cases with facial and meningeal angiomatoses associated with calcification of the cerebral cortex. He pointed out that the calcifications which had previously been presumed to be in the leptomeninges were actually in the cerebral cortex. The curvilinear calcifications seen by roentgenography were due to calcium deposits in the cortical convolutions and not due to calcified blood vessels in the leptomeningeal angioma.

Krabbe felt that the atrophy and sclerotic changes of the affected cerebral cortex in such cases were not just secondary to angiomas of the pia-arachnoid. The syndrome, he felt, consisted of angiomas of the face, angiomatous changes of the pia-arachnoid, and focal aplasia of the cerebrum, with probably secondary sclerosis and calcification of the aplastic portion.

* Wissing, O., cited by Krabbe.[16]

Further neuropathologic studies have revealed that not only is there an hemangiomatosis of the leptomeninges, dura mater, and even skull in this condition but anomalous vascular formations occur also in the cerebral cortex. Van Bogaert [13] concluded that the Sturge-Weber syndrome was essentially a cutaneous-meningeal angiomatosis, although in a large number of cases cerebral angiomatosis also occurred. Green [17] emphasized the presence of the angiomatous process in the cortical substance, as did Craig.[18] Lichtenstein [19] noted that "minor foci of hemangiomatosis may be found within the cerebral cortex and in the subcortical medullary substance."

Besides such vascular changes, marked alterations in the structure of the cerebral cortex (especially of the occipital lobe) have been recorded. Grossly, the affected cortex has been found to be atrophic, hardened, and shrunken. The affected cortex microscopically has been reported as showing loss of neurones and nerve fibers, extensive gliosis, "obliterative pericapillary fibrosis," deposition of minerals in the walls of capillaries, and accumulations of this material in the cortical parenchyma. It is these cortical changes which have aroused so much speculation. Krabbe [16] had felt that the focal cortical atrophy, gliosis, and mineral deposition was an aplasia, and he suggested that the developmental defect was thus both ectodermal and mesodermal in origin.

Van Bogaert [13] stated that the atrophic changes were in part the result of gliosis and in part due to a physicochemical alteration of the brain substance in the region of the vascular anomalies. The physicochemical changes favored the process of calcification. Thus calcification could proceed slowly. From this viewpoint the cortical changes of the Sturge-Weber syndrome were felt to be secondary to the mesodermal defect—thus an atrophy, not an aplasia. Peters [20] studied the brains of three patients of different ages (15 months, 8 years, and 32 years of age, respectively) and felt he could demonstrate the atrophic progression of the cortical lesion.

Craig [18] postulated that the gradually progressive destruction and shrinkage of the cortical tissue in these cases was probably secondary to the deposition of large amounts of iron and calcium in the vessel walls of the cortex and later in the interstitial substance as well.

Lichtenstein [19] suggested that the cerebral cortex changes may be due to a locally disturbed metabolism caused by venous stasis in the overly numerous pial veins. He stated that such a metabolic disturbance occurring early and vigorously would produce complete loss of neurones and reactive gliosis but that there would be little or no calcification. But if the metabolic effect was gradual, "calcification and/or ferrugination" of the affected cortex would occur.

The mechanism by which the mineral deposits occur in the angiomatous, atrophic cortex of cases of the Sturge-Weber syndrome has been speculated upon to a considerable degree. Eaves [21] and Craig [18] have shown that iron, as well as calcium, is present in these deposits. Alexander and Woodhall [22] have indicated that calcification of the nervous system is produced by long-standing inadequate blood supply. Baldauf [23] and Hanes [24] have shown the role of lipoid breakdown and the setting free of phosphoric acid in preparing necrotic tissue for calcification. Certainly all the elements necessary for such depositions are not known at this time.

More and more data have accumulated to favor an embryonal maldevelopment as a basis for the formation of the Sturge-Weber syndrome. This theory rests somewhat upon the work of Sabin [25] and Streeter.[26] The latter author divided the

development of the cerebral vessels into five stages: (1) establishment of a primordial vascular plexus, (2) differentiation of the plexus into the circulatory channels, (3) cleavage of these channels into three systems for the scalp, dura, and pia-arachnoid, (4) adjustment of the vessels to the growth of the head structures, and (5) final formation of the mature vessels.

The disturbance in the Sturge-Weber syndrome would seem to have to occur before the anterior plexus fuses with the middle plexus owing to the growth of the ear and alteration in the form of the brain (before the seventh week of gestation) and after the stage of differentiation of the primordial plexus into circulating channels (fifth week of gestation). Thus the embryonal interference would occur sometime during Stage 3, when there is a general cleavage of the vessels immediately surrounding the brain wall (the future pial vessels) from those belonging to the membranous skull (the dural and diploic vessels) and its integument (the scalp vessels). These embryologic observations make the relationship between occipital lobe angiomata and vascular nevi of the face understandable.

The varied associated lesions † would seem to favor a more generalized maldevelopment. Certain abnormalities of the eye seem not to be due to the vascular changes—for instance, exophthalmos, choroidal atrophy, glaucoma, and heterochromia iridis. Obesity, sexual infantilism, high arch of the palate, abnormally developed ears, and a flattened nasal bridge have been described frequently in these cases. Also, there are sometimes associated lesions which are more often found in the "neurodermatoses" (tuberous sclerosis and neurofibromatosis), such as cysts and congenital tumors of viscera, choroid plexus tumors, meningiomata, etc.‡

REPORT OF CASES

CASE 1.—R. McD., a 32-year-old white woman, was first seen on Sept. 24, 1948, because of paralysis of the right extremities and convulsive seizures. A "birthmark" on the left side of the face had been noted at birth.

At the age of 5 months, she was said to have had some sort of illness which had resulted in a paralysis of the right upper and lower extremities. Since then, she had had only slight return of function of the right extremities. Her "spells" had begun at this time and had continued to date. The seizures were described as consisting of clonic movements of the right extremities and face, but they often became generalized, with cyanosis, frothing at the mouth, and urinary incontinence. They occurred irregularly and were most often nocturnal.

The physical examination revealed a small white woman who was mentally retarded. She had a port-wine birthmark (vascular nevus) on the left side of her nose, forehead, and upper eyelid (Fig. 1). There was partial ptosis of the left upper eyelid, with impaired vision and abnormal blood vessels of the sclera of the left eye. The left pupil was larger than the right and did not react directly to light. The left optic nerve head was pale.

The neurologic examination disclosed a right spastic hyperreflexic hemiparesis. The right extremities were smaller than the left extremities. There were contractures of various muscles of the affected extremities. No sensory impairment was detected. There was a right central facial weakness.

The ophthalmologic consultant found no light perception in the left eye. Because of fullness of the left upper eyelid, the palpebral fissure was narrower than on the right. The external surface of the left globe was marked by prominent blood vessels, which below were large and radial in direction, while above, especially over the ciliary region, were smaller in a fine network. There appeared to be a left convergent strabismus. The left cornea was larger. The slit lamp

† References 1 and 27.

‡ References 28-30.

examination of the left eye showed several superficial corneal scars and two large blood vessels running radially on the iris. There were some specks of fine pigment on the anterior surface of the left lens.

Examination of the optic fundi showed a very marked glaucomatous cup on the left. Above and nasal to the left disc was an area of pigmentation about one disc diameter in size.

The gonioscopic examination of the left eye revealed a deep angle as well as the large blood vessels on the iris recorded above. There was a suggested small degree of exophthalmos of the left eye. Ocular tension of the left eyeball was increased (42 mm. Hg).

The roentgen examination of the skull showed an irregular calcification in the left occipital area. Its curvilinear configuration and location suggested calcification of the cortex of the brain. In addition, there was a large plaque-like calcification in the left frontoparietal region. This appeared to lie immediately beneath the inner table of the calvarium. Its position and appearance was that of a calcified subdural hematoma. The skull was asymmetrical, being smaller on the left side, a finding which was felt to be associated with hemiatrophy of the brain (Fig. *2*).

Fig. 1 (Case 1).—Note the nevus involving the left forehead, upper eyelid, and nose. The left upper eyelid looks thicker because of the nevus. Actually, the vascular anomaly extends beyond the midline on the nose.

The electroencephalogram revealed a gross difference in the level of the electrical activity of the two sides of the brain. There was very little activity on the left side. The dominant frequency was 6 cps, and, while more prominent from the occipital leads, it was also present from others, including the prefrontal leads. There were some 4 and 5 cps waves, and also some 8 cps waves. The pattern was considered to be definitely abnormal and was felt to be indicative of a subdural hematoma on the left side with diffuse brain damage of the other cerebral hemisphere as well.

The patient's convulsive seizures were controlled fairly well by anticonvulsant medication (sodium diphenylhydantoin, 100 mg. twice a day, and phenobarbital, 45 mg. at noon and 100 mg. before bed).

Comment.—This 32-year-old woman had her first manifestations of an intracranial lesion at the age of 5 months, in the form of a rather dramatic onset of a right hemiplegia and focal convulsions. The convulsive state and a right hemiparesis persisted. Her mental development was markedly impaired.

Fig. 2 (Case 1).—Roentgenogram of skull. *A*, posteroanterior view. Heavy curvilinear calcifications are seen on the left side, and a thin calcified plaque is evident along the left inner border of the skull. *B*, lateral view. The two calcified lesions are clearly seen here. The curvilinear calcification is in the occipital lobe, while the calcified subdural hematoma extends over the frontoparietal lobes.

She showed the fully developed syndrome of Sturge-Weber: nevus flammeus in the trigeminal distribution on the left side, a right hemiplegia, right-sided focal seizures, mental retardation, and vascular abnormalities of the left eye with unilateral glaucoma and blindness. Also, the skull roentgenograms showed irregular calcifications in the left occipital region and an asymmetry of the calvarium with hypodevelopment of the left side of the skull. In addition to these findings, there was roentgenologic evidence of a calcified subdural hematoma in the left frontoparietal region. As far as we can determine, a calcified subdural hematoma has never been previously noted in the Sturge-Weber syndrome. In light of the vascular nature of the cerebral lesion in the syndrome of Sturge-Weber, it would seem unusual that

Fig. 3 (Case 2).—Note the nevus involving the left forehead and the left side of the nose.

subdural hemorrhage has not been more frequent. One wonders whether the acute onset at the age of 5 months might not have been the development of this hematoma, with its destructive effect producing the hemiparesis and its irritative effect inducing the convulsive state. Unfortunately, because of the degree of the mental retardation, we were never certain of the sensory status of the hemiparetic side or of the extent of the visual fields.

CASE 2.—C. M., a 10-year-old white boy, was seen by one of us (G. A. S.) on May 17, 1951, because of uncontrolled seizures. A "birthmark" of the left forehead had been noted at birth.

At the age of 2½ years, with a febrile illness, he had a series of severe generalized seizures. About six months after this illness he began to have episodes of confusion, with staring into space. At times, he would cry out, grab for nearby objects, stiffen, or fall to the ground.

There had been three or four seizures in which his head had turned to one side (right?). Urinary incontinence occurred with some of the attacks. The spells had been increasing in frequency and severity.

There had been no subjective visual disturbance. A paternal aunt suffered from psychomotor seizures. The boy was in the fourth grade in school.

The physical examination disclosed a vascular nevus of the left forehead and nose (Fig. 3). There was no difference in ocular tension to finger pressure.

The neurologic examination revealed a 10-year-old boy who appeared to be of low average intelligence, who followed instructions poorly, and who was generally awkward. He was left-handed. The cranial nerves were intact. The child's gait was steady, and there was no swaying in the Romberg position. There was no disturbance of nonequillibratory coordination. Muscle status was unchanged. The sensory system was intact for the usual modalities. The reflexes were equal and active. There were no pathologic reflexes.

Routine studies of blood and urine revealed no abnormalities.

The skull roentgenogram disclosed an area of multilinear calcifications in the left occipital pole (Fig. 4). A left carotid angiogram did not add to these findings.

The electroencephalogram showed the general level of cortical activity to be 50 to 100 μv. A 9 cps alpha pattern was continuous on the right but disrupted on the left. There was also considerable 5 to 7 cps slow activity throughout. There were single spikes and sharp wave discharges which were seen only in the left frontal area. Hyperventilation produced bursts up to 400 μv of 3 to 4 cps single spike and sharp wave discharges bilaterally synchronous from all leads but especially marked from the frontal areas. Some of these bursts were accompanied by a jerk, synchronous with the cortical discharge.

The patient has been treated with various types of anticonvulsant medication, with poor control of his seizures.

Comment.—This child presented only part of the syndrome of Sturge-Weber—a vascular nevus in the distribution of the left trigeminal nerve, calcification in the ipsilateral occipital lobe, and convulsive seizures, but there was no ocular involvement, focal neurologic signs, or mental retardation. A few of his attacks were said to have included a turning of the head to the right, but otherwise the seizure pattern was not of a focal type. Only the facial nevus drew attention to the possibility of a cerebral vascular malformation.

CASE 3.—J. C., a white woman, was first seen on the Neurologic Service of the Hospital of the University of Pennsylvania on Oct. 8, 1928, at the age of 24 years. At that time she had a five-year history of episodes of inability to speak and right-sided weakness, but without loss of consciousness. These attacks usually began with a tingling, then a dead sensation in the fingers of the right hand. This sensation spread to involve the right upper and lower extremities. The attacks were usually followed by headache above the left eye.

She had been born with an extensive "birthmark" of the left face, neck, and lower extremity.

The physical examination revealed an extensive telangiectasia covering the left side of her face to the midline (Fig. 5). The mucous membrane of her left upper lip and cheek, of her left upper gums, of her left palate and posterior pharynx, and of her nose were involved by the vascular lesion. It extended onto the left side of her neck. Telangiectasia were noted on her left pinna, in her left external auditory canal, and even on the external surface of her left tympanic membrane.

The neurologic examination revealed the patient to be mentally clear. There were no objective neurologic abnormalities.

The ophthalmologic examination revealed only increased vascularity of the left retina.

The roentgenogram of the skull revealed no abnormalities, except a small pituitary fossa (anteroposterior, 8 mm.; depth, 4 mm.). She was readmitted to the neurologic service on Jan. 16, 1949, at the age of 44 years. Her attacks had continued to be of a similar character throughout the intervening years, but they had increased in frequency to one or two per week. She stated that sometimes her attacks were preceded by scotomata and accompanied by a sense of visual field constriction. Most of her seizures were followed by headaches.

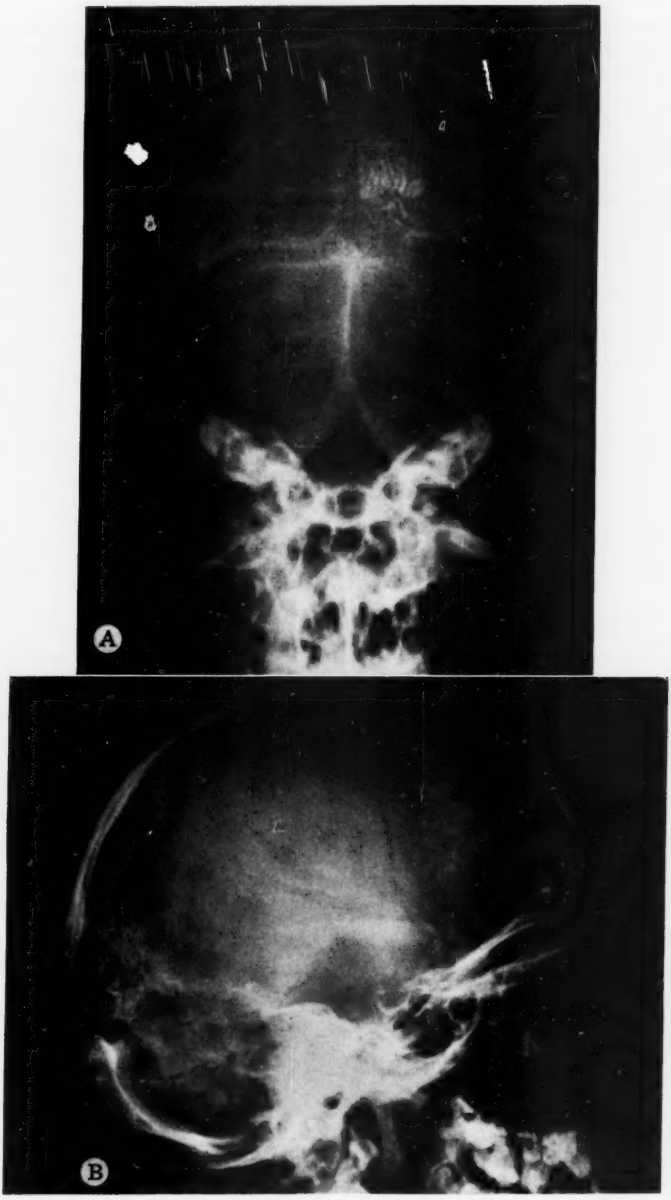

Fig. 4 (Case 2).—Roentgenogram of skull. *A*, anteroposterior view. The linear calcifications on the left side are clearly evident. *B*, lateral view. The intracerebral calcification is here seen to be at the occipital pole.

The neurologic examination at this time revealed a slight tremor of the right hand. Her left hand-grasp seemed stronger. Her hearing was slightly impaired on the left. The remainder of the neurologic examination was within normal limits. The ophthalmologic examination now showed the left cornea to be slightly larger than the right and the left iris lighter than the right. The right globe showed congenital melanosis. There was no evidence of glaucoma.

The skull roentgenogram showed additionally the pineal body to be 3 mm. closer to the right side, but not displaced in the saggital or horizontal planes. There was calcification along the inner table of the right frontal bone. This resembled the calcification seen in hyperostosis frontalis.

The left carotid angiogram revealed a normal vascular pattern.

Fig. 5 (Case 3).—The extensive nevus of the left side of the face and neck is readily apparent.

The electroencephalogram showed a lower level of activity on the left side of the brain. The general level of activity was 20 to 40 μv, with scanty 10 cps alpha rhythm of greater persistence and amplitude from the right occipital area.

She was discharged on anticonvulsant medication, and her seizures have been fairly adequately controlled.

Comment.—This patient had a much more extensive vascular nevus than our first two cases. Her vascular malformation spread far beyond the distribution of the trigeminal nerve. She, too, did not present the complete syndrome of Sturge-Weber. She showed no intracranial calcifications, no focal neurologic findings, and no mental retardation. Of localizing value was the right sensorimotor seizures with aphasia in a right-handed person—implicating the left cerebral hemisphere, ipsilateral to her facial nevus.

Her cerebral disorder did not manifest itself until the age of 18 years. The later findings of a tremor of the right upper extremity and slight weakness of the right hand-grasp, along with this delay of onset of her focal seizures, might argue for a progressive type of lesion.

CASE 4.—R. C., a 48-year-old white woman, was first seen on the medical service of the Hospital of the University of Pennsylvania in Feb., 1951, because of the onset of attacks of "numbness" followed by twitching or jerking movements of the left lower extremity in the summer of 1950. Her attacks usually began in the left foot, then involved the left leg and thigh, and later sometimes even involved the muscles of the left abdomen. These occurred once or twice a week; lasted for only a few minutes, and were followed by a sense of generalized tiredness and sleepiness. It was reported by her sister that in August, 1950, she was found to be unconscious in her sleep, with "foam" on her lips.

She had been born with "birthmarks" on both sides of the face, trunk, and limbs.

About 1948 she began having pain and swelling of the left lower extremity, although this limb was felt to have been larger than the right one all of her life. At the same time, she developed pain in her lower back.

The physical examination showed numerous flat hemangiomata and vascular nevi scattered over the skin of the whole trunk, limbs, and face, but there were more on the left side. There were also some pedunculated vascular lesions on the skin of the face. The left lower extremity was diffusely enlarged, especially below the knee, with slight pitting edema. There were a few partially thrombosed superficial veins in this extremity.

The neurologic examination revealed nothing significant at this time.

The opthalmologic examination showed congenital melanosis of the sclerae and congenital iris anomalies. There were no retinal abnormalities. The visual fields were suggestive of a right superior homonymous defect.

The roentgenogram of the skull showed the pineal shadow to be in the midline. No intracranial calcifications were observed.

A right carotid angiogram revealed nothing abnormal.

Intravenous urography and retrograde pyelography disclosed a slightly enlarged left kidney.

A phlebogram of the left leg showed an angiomatous group of deep-lying veins, with retrograde filling of some of the superficial veins.

The electroencephalogram showed diffuse marked slow-wave formation with hyperventilation. On activation with 50 mg. of diphenhydramine hydrochloride (Benadryl) intravenously, hyperventilation again produced runs of 5 to 6 cps slow waves, more prominent on the right side.

The patient was placed on anticonvulsant therapy, diphenylhydantoin sodium (Dilantin) and phenobarbital.

She was readmitted on Aug. 20, 1951, because of severe hematemesis and melana. The cause of the bleeding was not determinable roentgenographically or by gastroscopy.

She has continued to be followed in the neurologic outpatient department. Her attacks are as frequent as before, but they are now mostly of a focal sensory type. These attacks have persisted despite varied anticonvulsant regimens. A recent neurologic examination showed a weakness of the left lower extremity, with hyperreflexia but no pathologic reflexes. There has been no change in her electroencephalogram and no roentgenologic evidence of cerebral calcification. At this time she was felt to show a slight left exophthalmos.

Comment.—Of particular interest in this case were the excessive vascular anomalies of the skin and the late development of focal brain involvement. The patient did not have any demonstrable cerebral calcifications or mental retardation as seen in the classic syndrome of Sturge-Weber. Yet we feel that her case can be rightfully included, because of the occurrence of focal brain disease in a patient with facial vascular nevus. The progression of focal brain disturbance in the Sturge-Weber syndrome has been repeatedly noted and has been explained on the basis of impaired cortical circulation.

CASE 5.—S. L., a white female infant, was first seen on Jan. 21, 1947, at the age of 4 months, on the pediatric service of the University of Pennsylvania Hospital. She had been born on Sept. 2, 1946, with a pinkish-red discoloration of the skin of the upper trunk, neck, face, scalp, and left arm.

On Dec. 12, 1946, at the age of 3 months, she had her first convulsion. She had vomited the day before but was afebrile. The seizure involved her left upper extremity and left face. No residual weakness was noted. She had three similar convulsions that day. She was then free of seizures.

The physical examination showed an alert infant in a state of good nutrition. There was a "port wine" hemangioma, which became a deeper blue when she cried, over the upper chest and back, the neck, the face, the scalp, and the left arm. Uninvolved skin appeared as white areas on the forehead and occiput. Both conjunctivae were stained.

Fig. 6 (Case 5).—The nevus is evident by noting the patch of uninvolved pale skin in the middle of the forehead. This nevus involves both sides of the face; the pallor of the right hand also helps to emphasize the color difference.

The ophthalmologic examination showed good light perception, but the patient did not follow objects with her eyes. She tended to hold her eyes in right conjugate deviation. Her corneae were enlarged. The optic fundi revealed nothing abnormal. Ocular tension was borderline. Besides the finding of megalocornea, the ophthalmologic consultant suspected early buphthalmos.

Roentgenograms of the skull revealed no evidence of intracranial pathology.

She was readmitted to the ophthalmologic service on April 28, 1947, because of poor vision. At this time goniotomy was done, in an attempt to reduce the intraocular tension. Roentgen ray therapy was instituted and was effective in keeping the ocular tension within normal limits.

Nine days prior to her third admission, on Sept. 6, 1948, the child developed a fever, with vomiting and convulsions followed by generalized weakness. The seizures consisted of turning of her head and eyes to the right with flexion of her left arm and extension of her right, followed by generalized clonic movements over a two-hour period.

The physical examination on this admission brought out the fact that her vascular nevus also involved the buccal mucosa to the pharynx. The neurologic examination revealed a child who did not speak nor sit up well nor walk voluntarily but who had a normal placing reaction and equal use of her extremities.

A cerebrospinal fluid examination showed a grossly clear fluid, with 70 leucocytes per cubic millimeter and 187 mg. of protein per 100 cc. Again, no calcification was noted in the skull roentgenogram.

A pneumoencephalogram revealed the ventricular system to be well outlined and not enlarged or displaced. The subarachnoid pathways on the right in the parietal and frontal regions were increased.

An electroencephalogram showed a general level of activity of 50 to 100 μv. Slow waves, two to three per second, were more evident on the left and were predominantly frontal in location.

A bilateral carotid angiogram showed no evidence of an abnormal cerebral circulation.

The ophthalmologic examination now revealed the ocular tension to be within normal limits. The optic discs were of normal color but had deep cups. The retinal vessels were normal though tortuous.

The patient was discharged on anticonvulsant therapy, diphenylhydantoin.

Comment.—This patient, the youngest of our group, did not present the complete syndrome of Sturge-Weber. There were no intracerebral calcifications, no focal

Findings in Five Cases of Encephalotrigeminal Angiomatosis

Case	Facial Nevus	Focal Seizures	Hemiplegia	Mental Retardation	Ocular Abnormalities	Intracranial Calcification	EEG Changes
1. R. McD.....	+	+	+	+	+	+	+
2. C. M.....	+	Generalized & minor attacks	0	0	0	+	+
3. J. C.....	+	+	0	0	+	0	+
4. R. C.....	+	+	0	0	+	0	+
5. S. L.....	+	+	0	0	+	0	Borderline

neurologic signs, and no definite mental deficiency. She had more extensive ocular complications than our other cases. Of special interest here is the bilateral trigeminal hemangiomatosis and bilateral cortical irritative manifestations.

GENERAL COMMENT

We have described the findings in five patients in whom the clinical diagnosis of the Sturge-Weber syndrome (encephalotrigeminal angiomatosis) has been made. Our first patient manifested all of the classic signs and symptoms of the syndrome. Our other patients presented clinical pictures which varied somewhat from this standard grouping, yet we felt that they belonged in this syndrome. The major findings are listed in the Table, and a review of this shows that the most persistent findings were facial nevi, focal seizures, electroencephalographic changes, and ocular abnormalities. Of particular diagnostic value were the facial nevi (unilateral in three cases, bilateral in two) and the seizures (focal in four cases). The focal seizures were invariably contralateral to the facial nevus, when the latter was unilateral. As our cases illustrate, the classic signs and symptoms of the Sturge-Weber syndrome may be shuffled considerably from case to case. This variability has been suggested by reviews of published cases.

For instance, Greenwald and Koota [27] collected 82 cases of the Sturge-Weber syndrome from the literature up to 1936. Of their 82 patients, convulsions were the presenting symptom in 54 (65%) and finally developed in 82.9%. Hemiplegia was

present at onset in only nine cases, but it finally developed in 62.2%. Mental retardation was present in 60.9%, and ocular abnormalities, in 36.2%. The presenting symptom (other than the facial nevus) occurred at various ages in their 82 cases, as in our 5. The hemiplegia occurred at the age of 5 months in our first case, while convulsive seizures at 2½ years, 19 years, 48 years, and 5 months of age were the presenting symptoms in our other four cases. According to Greenwald and Koota, the symptoms are usually present in the first two decades of life. Only one of our patients developed symptoms after the age of 20.

In none of our cases were we able to demonstrate an increase or development of cerebral calcification over a period of time, as was noted by Anderson [31] and Davidoff and Epstein.[32] Only two of our five cases showed the central calcifications usually encountered. Lichtenstein [19] claims that these are not diagnostic in themselves.

None of our three patients who had carotid angiography showed abnormal cerebral vessels or retarded blood flow through the angiomas as reported by Green [33] and Hunt and Moore.[34] Moniz and Almeida Lima [35] reported a slowing of the cerebral circulation on the abnormal side but no anomalies in the areas of calcification. Bergstrand, Olivecrona, and Tönnis [36] have found angiography of no special value in the Sturge-Weber syndrome, except to rule out the presence of other blood vessel malformations.

The evidence of a progression in the signs and symptoms in this syndrome has motivated the removal of cerebral lesions, particularly when seizures could not be adequately controlled.§ There is still disagreement as to proper therapy. Many favor a more conservative approach, which consists mainly in controlling the seizures with anticonvulsant drugs.

Various surgical procedures have been recommended: the freeing of adhesions between the cerebral cortex and the meninges after ligation of the external carotid artery,[5] ligation of the common carotid artery alone,[38] ligation or cauterization of the vessels of the cerebral vascular anomaly,‖ incision of the dura mater and exposure of the cerebral nevus alone,[43] and excision of extensive areas of the involved cortex or brain.¶

Roentgen or radium therapy to the cerebral nevus has also been advocated by various persons, with or without decompression.#

The more radical surgical approaches would seem indicated only if proper anticonvulsant control has proved to be a total failure and also only if the deficit resulting from the surgery would not unduly surpass the deficit in the condition of the patient before operation. For instance, it would seem to us to be unwise to extirpate the temporal lobe or temporooccipital area of the dominant hemisphere, because of the resultant disabling aphasia.

Of particular interest is our first patient, who had a calcified subdural hematoma on the side of the cerebral angioma. Such an association of lesions apparently has not been noted before. It indicates another mechanism by which neural deficits may be produced in the Sturge-Weber syndrome.

§ References 22 and 37.

‖ References 39-42.

¶ References 36, 37, and 44.

References 12, 27, and 45-47 and Kohnstrom, G. L. S., cited by Weber.[7]

SUMMARY

Five patients are described who present the various signs and symptoms of the Sturge-Weber Syndrome (encephalotrigeminal angiomatosis).

One of our patients presented a hitherto unreported complication—a calcified subdural hematoma ipsilateral to the facial nevus and intracerebral calcifications.

Emphasis has been placed on the extreme variation of occurrence of the signs and symptoms comprising the Sturge-Weber Syndrome.

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VASODILATATION, LOWERED PAIN THRESHOLD, AND INCREASED TISSUE VULNERABILITY

Effects Dependent upon Peripheral Nerve Function

FRANK N. BILISOLY, M.D.
HELEN GOODELL, B.S.
AND
HAROLD G. WOLFF, M.D.
NEW YORK

SEVERAL observations suggest that neural activity may damage tissues by mechanisms other than those producing ischemia. The phenomenology of herpes zoster, with vasodilation, vesiculation, and necrosis of the skin accompanying damage of the dorsal and ventral horns, was at one time cited as evidence that nerve damage might secondarily cause skin injury. However, since the virus of herpes zoster has been demonstrated not only in the neural structures, but also in the skin, it is uncertain what part the nervous system effects play.*

The occurrence of herpes labialis following dorsal root section for trigeminal neuralgia supports the view that alterations in neural function may so change the environment of latent virus forms in the skin that they become active.[2] Thus, about 90% of persons who have had dorsal root section of the trigeminal nerve near the ganglion, including fibers subserving sensation of the lips, exhibit, as a sequel, herpes vesicles in the lips. When the lip skin area has been previously denervated, herpes lesions do not occur following dorsal root section. Such persons before the operation have a high titer of herpes antibody substance. Also in these subjects, after operation, herpes virus has been isolated from the vesicular fluid in the skin but not from the gasserian ganglion. Further, if dorsal root section be made at some distance proximal to the gasserian ganglion, i. e., if afferent fibers be cut in the brain stem itself, the incidence of herpes subsequently, according to Sweet,† is reduced to about one third. If, indeed, the skin lesion is more likely to occur when the nerve section is near the dorsal root ganglion, the possibility is raised that neurones in the ganglion stimulated by the surgical trauma initiate antidromic impulses and that the herpes virus, long latent in the skin about the lips, is thus activated by alterations in its environment.

Peripheral nerve damage in man may be accompanied by hyperalgesia and pain. Alterations in growth and repair cause the skin to become red and shiny, the nails

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From the New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College.

* References 1 and 2.

† Sweet, W. H., in discussion of Carton.[2]

ridged and brittle; even ulcerations and necrosis may occur. However, the dynamics of some of these "trophic" changes are hard to interpret, because the effects of infection and mechanical trauma to the skin cannot be completely eliminated.

Clinicians of the 19th century familiar with the numerous manifestations of tabes dorsalis described ecchymosis of the skin in painfully involved areas after long hours of severe "lightning" or root pains.[3]

Foerster,[4] using vasodilatation within the skin to show the dermal distribution of dorsal root fibers, noted that stimulation of the distal end of a cut dorsal root was followed by vasodilatation and painful sensations in the skin supplied by the particular dorsal root thus stimulated. For the pain to occur it was necessary for the dorsal roots on either side of the cut root to be intact. The reported pain might have resulted from electrical escape or from shunt effects to adjacent sensory roots near the site of stimulation. However, the possibility remained that a pain-threshold-lowering humoral agent was liberated in the skin by the root stimulation.

Lewis,[5] experimenting on cats, found, as had others before him, that when the distal end of the cut dorsal root was stimulated vasodilatation occurred in the foot pad of the cat. In addition, he noted a delay in its appearance if circulation to the part was occluded. Also, it long outlasted the usual vasodilatation (reactive hyperemia) that followed the return of the circulation. This evidence supports the second possibility mentioned above, i. e., that neural processes may alter the tissue subserved, presumably by a liberated humoral agent, so as to modify circulation and cell permeability and in turn to stimulate afferent nerve end-organs.[5]

Another direction was explored by those interested in hypnosis and suggestion. "Blister" formation in the skin of suitable subjects as a result of alterations in mental state has been reported. Such alleged changes presumably involve peripheral neural pathways, but the mechanism has not been investigated.[6]

Kindred topics have been studied in the New York Hospital.‡ During periods of adjustment to threats, damaging effects in the mucous membranes were observed. Wolf and Wolff [9] were able to demonstrate such alterations in the gastric mucosa; Holmes and co-workers,[10] in the nasal mucosa; Grace and co-workers,[11] in the colon mucosa, and Straub and co-workers [12] and Duncan and Taylor,[13] in the bladder and vaginal mucosa. Conspicuous were vasodilatation, edema, diapedesis, hemorrhage, erosion, increased friability of tissue, and lowered pain threshold. Added to these phenomena were alterations in secretion, and in the intestine there was altered absorption. These responses, when excessive in amount and duration, were exhibited as gross tissue damage.

Although tissue damage was striking in these mucous membranes, this did not establish that all the effects observed were the sequelae of direct nervous action. It is not possible in all instances to cut relevant peripheral nerves and thus detect the pathways by which effects are induced. Changes in quality and concentration of secretion, in motility, and in the bacterial contents of the intestine may be pertinent. Further, endocrine agents may participate in the tissue changes. Thus, moderate amounts of corticotropin (ACTH) liberated as a result of anterior hypothalamic excitation and pituitary stimulation might affect gastric mucous membranes. Even

‡ References 7 and 8.

though this mode of action is less likely during brief periods of stimulation, these models are technically too complicated for studying the dynamics of nervous system participation.

Observations on subsurface structures are also relevant. Thus, lowered pain threshold and increased tissue vulnerability accompany the characteristic vasodilatation in subcutaneous tissue during vascular headache attacks.§ Morover, these effects are reversed to preattack levels by arterenol (Nor-epinephrine) and other vasoconstrictor agents.|| Again, how and which peripheral nerves are involved in the changes has not been defined.

Attempts were made by Graham [17] to understand the nature of the local skin changes relevant to pain, burning, and itching experienced with urticarial reactions. These studies showed that with vasodilatation of the minute vessels of the skin accompanying threats and symbolic assaults the permeability of the minute vessels was altered and edema ensued with itching and burning pain. Vasodilatation in the skin appeared with extraordinary promptness in response to specific types of threatening symbols, and thus it seemed extremely likely that the reaction was neurogenic. The vulnerability of the skin to a variety of different stimuli (chemical and mechanical) could be dramatically increased; also, this state of increased vulnerability was readily reversible.

Hardy, Wolff, and Goodell ¶ showed that the adequate stimulus for pain in the skin is the damaging of tissue. Thus, regardless of the temperature of the skin at the time of applying a thermal stimulus, when, as a result of the latter, a skin temperature of 44 to 45 C. was attained human subjects complained of pain. It was pointed out that protein alterations occurred at this level, and it was inferred that when such alterations occurred in the vicinity of sensory endings a disturbance was set up which resulted in the initiation of afferent impulses ultimately interpreted as pain. Most recently, Lipkin and Hardy [20] further illuminated the relation between tissue damage and pain threshold by showing that a measured amount of noxious stimulation, as expressed in time and intensity of ultraviolet radiation of the skin, resulted in predictable amount of lowering of pain threshold. The greater the damage, the further (within limits #) was the pain threshold lowered. Thus, from the usual 44 to 45 C. threshold, pain was elicited at 36 to 37 C., the level depending on the amount of noxious stimulation and damage. With more accurate examination, there is evidence of a close relationship between the damage of tissue and the pain threshold and also the amount of noxious stimulation to which tissue is exposed and the degree of pain-threshold lowering.

Goodell, Graham, and Wolff [21] then further demonstrated that a variety of agents and procedures that induced vasodilatation in the skin also lowered the pain threshold. Reflex vasodilatation was produced in the skin of the thorax and hand by immersing the lower extremities in water at 43 C. and simultaneously drinking hot fluids. Pain threshold measurements were found to be lowered in the area of reflex vasodilatation. The latter could not be attributed to the heating of the skin alone. Thus, regardless of the stimulus or mechanism involved, the pain threshold was temporarily lowered when the minute vessels of the skin dilated. But, again,

§ References 14 and 15.

|| References 15 and 16.

¶ References 18 and 19.

I. e., short of neural destruction.

if and how peripheral nerves were involved in these reactions were not explored, even though these experiments did show that reflex effects may alter the vulnerability of skin. Hence, to ascertain whether peripheral nerve effects per se could result in increased tissue vulnerability new information was necessary.

Because of its well-defined neural components, the triple response to injury in the skin was employed to explore peripheral nerve influence on tissue vulnerability. Lewis [5] defined the triple response as follows: (1) a circumscribed vasodilatation at the site of injury, (2) edema about the latter, and (3) more widespread vasodilatation, or flare. Evidence on which Lewis and his colleagues based their views on the liberation of a chemical substance to explain the flare of the triple response was obtained by comparing the reaction of the skin of the arm to a heavy stroke when the circulation was normal and when the arterial flow was occluded by inflating an arm band. In the normal arm the vascular reaction lasted some 10 minutes, but that occurring in the occluded arm lasted for as long as 25 minutes. When the circulation was readmitted the flush faded in about 10 minutes. The events were interpreted as being due to the release of a vasodilator substance by the damaged tissue which could not escape from the tissues of an arm when the circulation was occluded. A triple response to skin injury occurs only in skin with intact dorsal root fibers. When these fibers are allowed to degenerate, the response in the skin to local injury is far more limited, i. e., only Responses 1 and 2 are present, and Response 3, the flare, is absent. Lewis inferred that the flare results from reflexes initiated at the site of primary damage of the skin. These latter are probably axonal and do not necessarily involve the dorsal root ganglion or the central nervous system. If it could be demonstrated that concurrently with such local reflex vasomotor phenomena the pain threshold is lowered, such data would support the view that the reflex effects also alter the integrity of tissue about afferent nerve endings.

Attempts were then made to ascertain the exact relation between vasodilatation, pain threshold, and tissue damage of the area within the flare of the axone reflex.

EXPERIMENTAL PROCEDURES

Series 1

Demonstration by Thermal Dolorimetry of Lowered Pain Thresholds in Flare Zone of Axone Reflex on Forearm.—Eight spots about 1 cm. in diameter were outlined and numbered around oval areas about 12 cm. long and 6 cm. wide on the volar surface of the left and right arms. The eight spots were painted with India ink and allowed to dry. Skin temperatures were measured in each spot on both arms, and the pain threshold was ascertained with thermal radiation from a dolorimeter. Next, in the center of the oval area on the right arm, a noxious agent (0.1 cc. of histamine phosphate) was injected intradermally. Within 10 minutes the flare had spread to involve Spots 2, 4, 5, 6, 7, and 8 in subject F. B. Skin temperatures in these spots were elevated about 1 to 1.5 degrees (C.).

A draft of cool air was then directed through a paper funnel from an electric fan to these spots, and pain thresholds were measured when the skin was cooled to levels of temperature approximating control measurements before the onset of the flare.

In subject F. B. measurements were made in Spots 5 and 8 because these two spots were completely included in the flare, whereas the others were only partially included. Table 1 and Figure 1 show the lowering of pain threshold in the flare zone of the axone reflex with skin temperatures lowered to approximate control levels.

In subject H. G. the same procedure was repeated. All test spots were well within the zone of flare, as shown in Table 2.

Comment: In the flare zone of the axone reflex pain threshold, as measured by the thermal radiation method, was significantly lowered during the phase of spread of the flare. Even though the skin was cooled to its control level just before a measurement, the threshold remained lowered, indicating that the effects ascertained were not dependent upon the elevation of skin temperature due to vasodilatation.

SERIES 2

Demonstration of Lowered Pain Threshold in Flare Zone of Axone Reflex That Included Eyelid.—(*a*) By Thermal Dolorimetry: Because the "flare" area in the skin was sometimes so close to the site of injury, and hence could possibly result from diffusion of products of injury, an experiment was devised that would

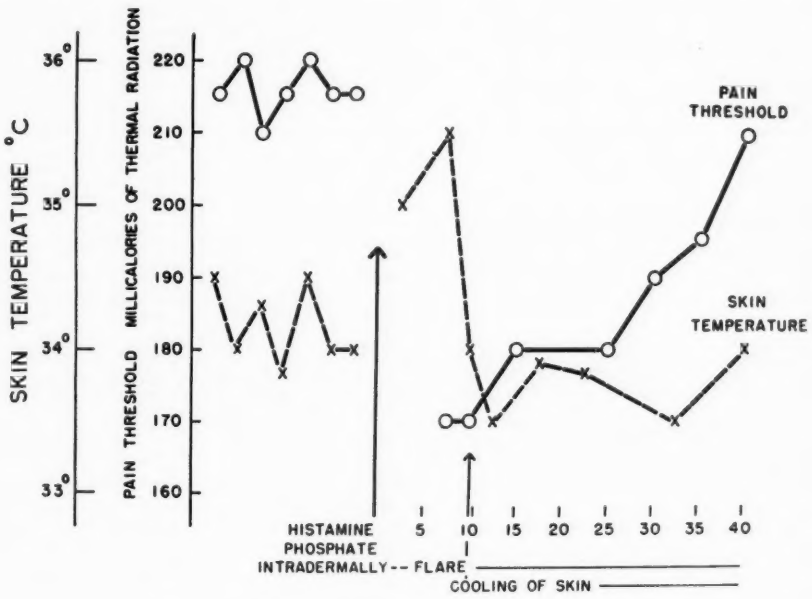

Fig. 1.—Reflex vasodilatation and lowered pain threshold.

TABLE 1.—*Lowered Pain Threshold in Flare Zone in Subject F. B.*

	Control (Left) Arm				Test (Right) Arm			
	Temperature		Pain Threshold *		Temperature		Pain Threshold *	
	Spot 5	Spot 8	Spot 5	Spot 8	Spot 5	Spot 8	Spot 5	Spot 8
Controls at 10:50	34.2	34.2	220	220	33.8	34.5	210	210
Histamine at 11:09	....	....	...	...	....	....	...	...
Flare developing from 11:17 to 11:30	....	....	...	...	35.2	34.5	...	...
Cooling at 11:35	....	....	...	...	....	....	...	...
11:40	....	....	...	...	33.8	34.5	180	180
11:45	....	....	...	...	33.5	33.2	...	...
11:55	33.3	33.0	220	220	33.5	32.5	185	180

* Pain threshold is measured in millicuries per second per square centimeter.

have the advantage of a considerable separation between the site of injury and the outer limits of the flare zone. The axone reflex was initiated by injury of the mucous membranes of the nose, and the reddened conjunctiva and lids were selected for the testing.

In two subjects (F. B. and F. S.) a round spot of India ink about 3/8 in. (0.95 cm.) in diameter was painted on the right eyelid. The pain threshold was measured by the thermal radiation method on the blackened area. For subject F. B. the pain threshold of the eyelid was 210 mc. per second per square centimeter, and for F. S. it was 200 mc. per second per square centimeter. Saturated sodium chloride solution was then instilled in the right nostril; this was followed by

TABLE 2.—*Results in Subject H. G. of the Test Procedure Used in Table 1*

		Left (Histamine) Side		Right (Control) Side	
	Skin Spot	Skin Temperature	Pain Threshold *	Skin Temperature	Pain Threshold *
Control 2:30 p. m.	1	33.3	215	32	210
	2	33.0	225	32	210
	3	33.0	225	32	220
	4	34.3	210	32.4	220
	5	33.6	225	32.3	220
	6	33.6	220	32.9	220
	7	33.8	220	33.0	220
	8	33.5	210	32.8	210
Histamine 2:50 p. m.	..	....	...	....	...
Flare 3 to 3:10 p. m.	1	35.0	185	33.6	215
	2	34.2	185	33.2	210
	3	34.8	180	33.5	220
	4	35.0	170	34.6	210
	5	35.1	180	34.2	215
	6	35.6	145	34.2	215
	7	35.4	180	34.2	210
	8	34.0	170	33.8	210
Cooling 3:10 to 3:15 p. m.	..	....	...	....	...
3:15 to 3:30 p. m.	1	35.0	170	Not measured	
	2	32.7	180	Not measured	
	3	33.5	190	Not measured	
	4	34.1	170	Not measured	
	5	34.0	170	Not measured	
	6	34.0	155	Not measured	
	7	34.5	155	Not measured	
	8	34.1	190	Not measured	

* Pain threshold is measured in millicuries per second per square centimeter.

pain, engorgement, secretion, and obstruction in the nose and by vasodilatation elsewhere, as evidenced by reddening of the conjunctiva of the eye and the eyelid. The pain threshold of the reddened lid was measured three minutes later in F. B. and found to be lowered to 170 mc. per second per square centimeter. Five minutes after the instillation of salt the pain threshold of the eyelid in F. S. was lowered to 160 mc. per second per square centimeter.

Skin temperature and the amount of thermal radiation inducing pain in the skin are closely linked (threshold pain being evoked when skin temperature is at the critical level of 44 ± 1 C.). Also, with vasodilatation in the zone of axone flare skin temperature is elevated from 0.5 to 2.0 degrees (C.). With each 1 degree (C.) change in skin temperature there is an estimated approximate difference of 20 mc. in the intensity of the thermal stimulus which will raise the skin to the critical

level of 44 ± 1 C.* In the previous experiment it was demonstrated that pain threshold was lowered despite cooling of the skin, demonstrating that in the presence of vasodilatation the critical temperature at which pain is evoked in such skin is itself lowered. However, the following procedure was utilized to demonstrate that lowering of the pain threshold in a zone of axone reflex is not dependent on a change in skin temperature. Pain threshold as tested by a von Frey hair would be virtually independent of skin temperature, even though the interpretations of the result are much less simple.

(*b*) By von Frey Hair: With the subject's eyeball rolled toward the outer canthus, the conjunctiva of the eyeball between the cornea and the inner canthus was tested with a von Frey hair until such a length was found which, when touched to the conjunctiva, elicited a sensation of touch in 4 to 6 out of 10 trials. Saturated saline solution was then instilled into one nostril on the same side as the tested eye. This elicited intense pain, profuse watery discharge, engorgement of the nasal mucosa and nasal obstruction, and a concomitant reddening of the eyelids and conjunctiva and watering of the eye. Five minutes later the eye was again tested with the same length of von Frey hair. This procedure was performed twice in subject F. N. B. and once in subjects H. G. and H. G. W., and in each experiment the von Frey hair of the same length which in the control situation had elicited touch in only 4 to 6 out of 10 trials and no pain now elicited a sensation in 8 out of 10 trials, of which 4 were pain and 4 were touch. Within 18 to 20 minutes injection of the conjunctiva was no longer evident, and pain was no longer elicited by the von Frey hair.

Though not a satisfactory method of assaying pain threshold, the fact that the pain threshold was lowered in the zone of vasodilatation suggests that a primary hyperalgesia actually existed. A more satisfactory method was employed in the next series of observations.

SERIES 3

Demonstration by Measurement of Hair-Pull Pain of Lowered Pain Threshold in Flare Zone of Axone Reflex on Forearm and Leg.—For the purpose of using means other than heat and von Frey hairs for noxious stimulation, the pain threshold in the zone of axone flare was ascertained by means of the hair-pull pain method.

Method: The apparatus is shown diagrammatically in Figure 2. A single hair of the subject is attached to the device by means of a small clamp. Traction at a steady rate of increase is placed upon the hair by a string, pulley, and reel system operated by the observer. A fine elastic thread is fixed at its upper end to an arbitrary scale panel and at its lower end to the hair through the string and clamp. Thus, as the hair is pulled upon the elastic thread is stretched.

The subject is instructed to concentrate on the area of stimulation and to report at the instant that a sensation of pain is perceived. This sensation is that of a slight "pulling," rising to a distinct "prick" of pain.

The length to which the elastic thread is stretched at the pain threshold is noted on the scale.

The amount of traction necessary to elicit threshold pain is usually not sufficient to extract the hair, and so the same hair may be used for repeated readings. The end-point thus ascertained for a given hair is found under standard conditions to be predictable within narrow limits.

The length to which the elastic thread was stretched at the pain threshold was noted on the scale. For a control pain threshold, before introducing a test situation, five such readings were made, at two-minute intervals. The scale was so drawn that, with trained subjects, the five control readings varied no more than ± 0.5 unit. To damage the skin locally and thus initiate an axone reflex flare, histamine phosphate (0.1 cc. of a 1:1000 solution) was injected intradermally at a distance of approximately 2 cm. from the attached hair. The pain threshold was measured by pull on the hair, at two- to five-minute intervals.

* References 18 and 19.

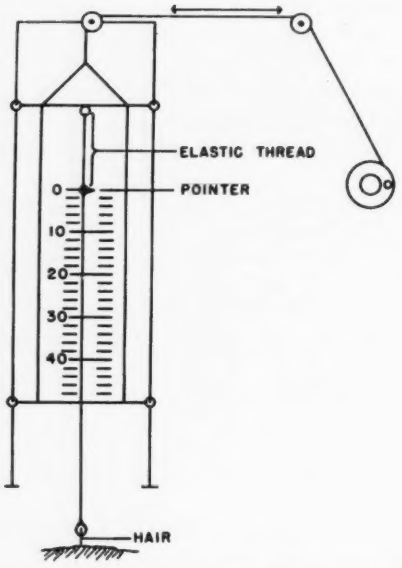

Fig. 2.—Device for measuring pull on a hair at pain threshold.

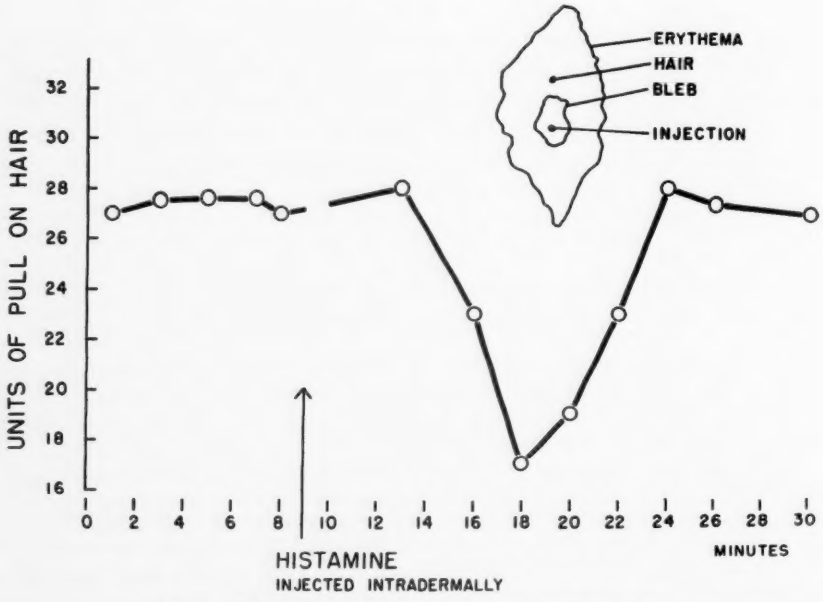

Fig. 3.—Reflex vasodilatation and lowered pain threshold.

Results: In nine experiments in five subjects a hair on the volar surface of the forearm was used for testing, and in eight experiments in three subjects a hair on the lower leg was used. Because the extent and shape of the flare resulting from the intradermal injection of histamine could not be predicted, the test hair in seven experiments was not satisfactorily included in the reddened area. Also, in three subjects the hair was involved in an edematous pseudopod extending from the bleb at the site of injection. Thus, 10 of the 17 experiments were unsatisfactory and measurements of pain threshold could not be made. In the remaining seven experiments a lowering of the pain threshold was demonstrated in the zone of axone reflex, as shown in Figure 3 and Table 3.

Comment: From these observations it is inferred that the pain threshold as ascertained by the hair-pull method was lowered in the flare area of the axone

TABLE 3.—*Pain Threshold Measured in Arbitrary Units of Traction on a Hair in Zone of Axone Reflex (Flare)*

Subject	Control Pain Thresholds	Pain Thresholds in Zone of Flare After Indicated Minutes								
		5	7	9	11	13	15	20	30	45
N. R.	25, 25, 25, 25, 25	25.0	23.5	24.0	23.0	22.0	22.0	22.0	23.5	24.0
A. O.	18.5, 18.5, 18.0, 18.0, 18.5	....	18.0	....	18.0	16.5	16.0	16.0	19.0	18.0
H. G. W. 12/22/53	28, 27, 27, 27, 27	24.0	20.0	....	22.0	24.0	23.5	26.5	27.0	27.0
H. G. W. 12/29/53	27, 27, 27, 27	28.0	23.0	17.0	19.0	23.0	28.0	27.5	27.0	....
B. B. 12/29/53	27.0, 26.5, 27.5, 27.0	22.0	22.0	21.5	....	27.0	28.0	....	26.5	....
H. G. W. 12/31/53	28.0, 27.0, 27.0, 26.5, 27.0	27.0	26.5	25.0	26.0	27.5	27.5	....	27.0	....
H. G. W. 12/28/53	Unsatisfactory control	....	29.0	....	23.0	....	19.0	20.0	28.0	....

reflex. They confirmed the indications of lowered pain threshold given by measurements of pain threshold by thermal dolorimetry and by von Frey hairs in the previous Series 1 and 2.

SERIES 4

Demonstration that Lowered Pain Threshold in Flare Zone of Axone Reflex is Manifestation of Tissue Damage and Increased Vulnerability.—(*a*) Demonstration by Use of Heat: To answer the question, "Is the vulnerability of the skin to injury in the flare zone of the axone reflex increased?" the following procedures were carried out in four subjects in 11 experiments. The subjects were H. G., H. G. W., F. N. B., and R. J.—three men and one woman. In all the experiments widespread vasodilation was evoked in confluent zones of axone reflex by injuring the skin with histamine phosphate (0.1 cc. of a 1:1000 solution) intradermally at three sites about 3 cm. apart on the longitudinal axis of the volar surface of the forearm. In nine of the experiments in four subjects, eight to ten small round spots of India ink were then painted on the skin so as to be well separated from each other but to be included within the zone of axone reflex. The same number of spots in exactly the same pattern was painted on the other, control, arm. In 7 to 10 minutes after injection of the histamine, when the axone reflex flare was widespread but still in the stage of spreading vasodilatation, two blackened spots on each arm were exposed to each of the following four intensities of thermal radiation for three seconds: 300 mc., 330 mc., 365 mc., and 400 mc. Each of these intensities of thermal radiation when applied to blackened skin for three seconds is known to damage skin under ordinary circumstances. A few minutes after the noxious stimulation on all the spots was completed, the India ink was carefully

washed off with cotton and lukewarm soap suds, gently sopping the areas to avoid trauma. The sites of exposure to noxious stimulation were then examined at intervals for the next several days, and the degree of damage at each site was estimated using a rating of 0 to 8 +.

Because the skin temperature was slightly elevated in the zone of the axone flare, attempts were made in three experiments to cool the vasodilated area to the temperature of the control arm by a directed draft of air, just before the skin was exposed to noxious stimulation by heat.

There was significantly more skin damage in the zone of axone reflex than in similar areas on the control arm as the result of exposure to similar intensities of noxious stimulation. These differences appeared greater with the passage of time and were most marked 48 hours after thermal injuries (Fig. 4). Two attempts at cooling the skin were unsatisfactory, because the skin was cooled as much as 10 degrees below the temperatures of the control arm and later no difference in the amount of damage on the two arms could be detected. On the other hand, these failures are not without significance, since in spite of the cooling the amount of damage from thermal radiation was similar to that of the control arm.

DEGREE OF TISSUE DAMAGE	ERYTHEMA — INTENSITY OF RADIATION IN MILLICALORIES/3 SEC						CONTROL — INTENSITY OF RADIATION IN MILLICALORIES/3 SEC					
	380	360	340	320	300	TOTAL	380	360	340	320	300	TOTAL
4+	𝍸	𝍸				8	𝍸					2
3+	𝍸	𝍸	𝍸			7	𝍸	𝍸				4
2+	+	𝍸	+	𝍸		6	𝍸	+				4
1+			𝍸	+	+	5		+	𝍸	𝍸		5
0			𝍸	𝍸𝍸	𝍸𝍸	14	+	𝍸𝍸	𝍸𝍸	𝍸𝍸	𝍸𝍸	25

READINGS MADE 48 HOURS AFTER EXPOSURE TO THERMAL RADIATION

Fig. 4.—Increased vulnerability of tissue in zone of axone reflex.

(*b*) Demonstration by Use of Faradic Current: In two experiments on subjects H. G. W. and F. N. B. the skin in the zone of axone reflex and in a similar pattern of sites on the control arm was noxiously stimulated by faradic current in a series of four increasing intensities. Two sites on each arm were stimulated with each intensity. The sites of damage were examined at 12-hour intervals for the next 12 days.

The differences in the amount of damage in the zone of axone reflex and in similar areas of the control arm were striking. They are summarizd in Figures 5 and 6, as they appeared during a period of 12 days after injuries by faradic stimulation.

(*c*) Demonstration by Use of Chemical Agent: Trichloroacetic acid in dilutions of 8.6%, 7.5%, 6.6%, and 5.0% was used as a traumatizing agent. H. G., F. B., and H. G. W. were the subjects; on the volar surface of the left and right arms four spots 5 mm. in diameter were surrounded with black petrolatum to insure containment of the 0.05 cc. of acid solution to be applied later.

In the center of the square formed by the four spots on the right arm histamine phosphate (1:1,000), 0.5 cc., was injected intradermally to induce an axone reflex flare. Four minutes later the flare had spread to include the four spots. Measured amounts of the four dilutions of acid were then applied in series to the spots on the left and right arms, the left arm serving as

control. After the application of the acid, 0.05 cc. amounts to each spot, the subject reported an intense itching sensation on both arms, which was more intense on the test arm and became a burning sensation. Fifteen minutes after its application the arms were washed to remove the corrosive agent, and the spots were examined after 2 hours, 16 hours, and 24 hours and at daily intervals thereafter for six weeks.

In each of the subjects at the end of two hours after the application of the acid to the four skin spots on the two arms there was marked reddening and swelling

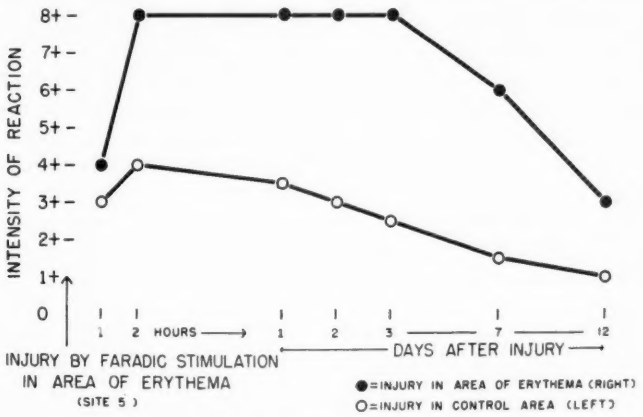

Fig. 5.—Increased vulnerability of tissue in zone of axone reflex.

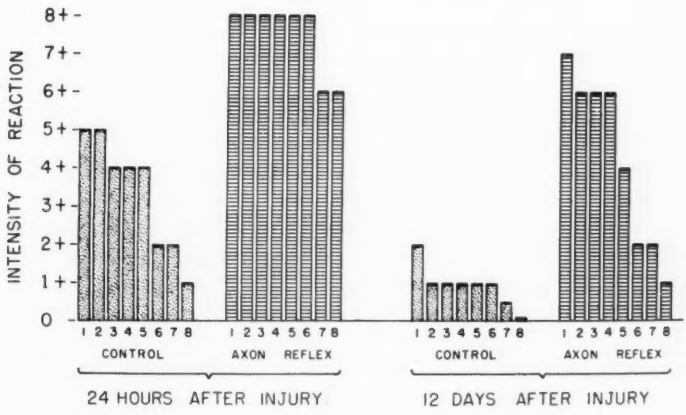

Fig. 6.—Increased vulnerability of tissue in zone of axone reflex.

surrounding all spots on the right test arm, it being somewhat less on Spot 1 (that of the highest dilution of acid). There was a lesser degree of reddening surrounding the spots on the control arm and less swelling as compared to the test arm.

Sixteen hours later, swelling was gone and eschars were beginning to form over the spots. There was more reddening surrounding Spots 2, 3, and 4 on the test arm than on the control arm. Spot 1, (that of the highest dilution) showed the least reaction but was more evident on the test arm.

During the subsequent two weeks there appeared to be thicker eschars, particularly in Spots 2, 3, and 4, on the test arm than on the control arm. During the third week after injury the eschars on both arms peeled off spontaneously, revealing in two experiments in one of the three subjects (H. G.) at this late stage less residual inflammation on the test arm.

Comment: It is evident that the intensity of reaction both shortly after injury and at intervals over 12 days was distinctly greater in the flare zone of the axone reflex than in the comparable control areas. Hence, regardless of the method used in injuring the skin, the vulnerability was far greater in the flare area of the axone reflex and less injurious stimuli became more noxious.

Acceleration of the repair was suggested in one of the three subjects in two experiments in the studies with trichloroacetic acid. Although the initial damage in all three subjects was more conspicuous when the skin was injured in the flare zone, the late appearance of the lesions on the control as compared with the test tissue in one subject indicated that healing was hastened in the flare area. This supports the view that the greater vulnerability of tissue in the axone reflex zone is a part of an adaptive arrangement not only to circumscribe the effects of injury but also to enhance repair.

GENERAL COMMENTS—NEURAL FACTORS IN INFLAMMATION

Florey [22] in a current and lively review of inflammation has assembled many of the pertinent data on this relationship. Among the first to suggest that an axone reflex was involved in the vascular dilatation of inflammation was Bruce,[23] who, in studying the effects of mustard oil on the conjunctiva of the rabbit, found that vascular dilatation was much reduced if the conjunctiva was previously cocainized and, also, that if the nerves to the conjunctiva had been cut and given time to degenerate dilatation failed to occur. Bruce considered that these effects were due to the abolition of an axone reflex. Similarly, Krogh † noted that the capillary dilatation that followed the application of iodine to a frog's tongue was abolished if the sensory nerve endings had been paralyzed by cocaine. From these and other experiments he also concluded that axone reflexes were involved in the inflammatory phenomena.

Lewis [5] with Grant, as cited above, during their analysis of the "triple response" showed that a red central area surrounded by a brighter red flare appeared after the application of a test tube containing hot water to normal skin but that if the sensory nerves to the skin had been cut some days before the experiment, during which the nerve fibers had degenerated, only the central red area developed. If the experiment was done within six or seven days of cutting the sensory nerve and before the completion of nerve degeneration, the peripheral flare could still be seen. These results were logically explained by the mechanism of the axone reflex.

Cohnheim [26] held the view that the vasomotor nerves play no part in the development of inflammation, but their influence has been demonstrated. The following, quoted from Florey, [22] is a résumé of the topic written by Adami in 1909.[27]

> [The external ear of the rabbit] has a double nerve supply through the auriculars (major and minor) from the cervical plexus and the sympathetic branches from the superior cervical

† References 24 and 25.

ganglion: stimulation of the former leads to dilatation of the ear vessels (vaso-dilator action), of the latter to contraction of the same (vaso-constrictor). If, as shown by Samuel, the sympathetics be divided on the one side, and the auricular branches upon the other, the ear vessels of the former side become widely dilated (unimpeded action of vaso-dilators), and those of the latter markedly constricted. Under these conditions, if both ears be subjected to the action of water warmed to 54° C. there is a characteristic difference in their reaction. In the organ deprived of sympathetic influence the congestion and hyperaemia become yet more pronounced: an acute inflammation sets in which rapidly proceeds to recovery. In the opposite ear, with its constricted vessels, no hyperaemia is set up; but there is stasis, and gangrene may supervene. These results have been confirmed by Roger who, taking a rabbit and dividing the sympathetic on one side, and then inoculating both ears with like quantities of a culture of the streptococcus of erysipelas, found that the erysipelatous process manifested itself much more promptly upon the paralyzed side, and came to an end at an earlier date. The reverse was the case when the auriculars of the one side had been divided: here the process was of slower development than on the intact side, and of slower course, resulting in mutilation of organ. Further confirmation is afforded by the researches of Meltzer and Meltzer.

The inference to be drawn from these observations is that section of all the nerves passing to the rabbit's ear permits the inflammatory process to run a more rapid course: section of the sympathetics (vasoconstrictors) alone has the same effect; while the uncontrolled action of the sympathetics after section of the auriculars (vaso-dilators) hinders or prevents the manifestation of the ordinary processes of inflammation, and by preventing the destruction or removal of irritant matter favors necrosis of the tissues.

Florey also states that the work of Samuel and Meltzer and Meltzer, showing that cutting the cervical sympathetic nerves enhances the effects of inflammation, was confirmed by others. At this early date, however, no suggestion was rendered as to the presence of a pain-threshold-lowering substance associated with the vasodilatation.

Although the evidence presented in this report demonstrates the participation of dorsal root fibers in vasodilatation, lowering of the pain threshold, and tissue vulnerability in the skin, it is probable that other than dorsal root fibers can induce similar changes. For example, the lowered pain threshold in the skin of the forearm during reflex vasodilatation from immersion of the feet in hot water suggests that autonomic fibers may participate in the changes.

It is possible that other neural structures and neurohumoral agents may be involved. Stimulation of the posterior portion of the hypothalamus increases secretion and induces vasomotor changes in the mucous membranes of the stomach. These changes are mediated through the vagus nerve. On the other hand, stimulation of the anterior portion of the hypothalamus brings about comparable changes in the stomach in which the vagus plays no part. The changes in the latter instance are dependent upon elaboration of humoral agents by the anterior pituitary gland. Both neural and humoral effects are thus pertinent to increased vulnerability of the gastric mucous membranes.

The demonstration that with threatening symbols there may be induced urticarial reactions, with local vasodilatation, edema, lowered pain threshold, and itching and burning pain, strongly suggests that processes similar to those that are shown to occur in the zone of axone reflex may be pertinent in the genesis of urticaria.

To date, antidromic impulses are not known to be relevant to physiological function. Yet relatively minor changes within the cord make possible the demon-

stration of antidromic impulses in adjacent roots on vigorous stimulation of any single dorsal root.‡

In all events, it follows from these experiments that the peripheral nervous system can further the disintegration of tissue it subserves.

What could be the advantage to an organism of having neural integrative devices that enhance tissue destruction? The view is proposed that such adaptive processes enhancing inflammation are relevant to the protection of the whole organism at the cost of the integrity of a part. Man includes among his protective adaptive devices processes initiated along with vasodilatation that so alter the vulnerability of tissue that heretofore non-noxious stimuli become noxious and painful and mildly damaging stimuli become more injurious. Such devices are sometimes used inappropriately and may then result in symptoms and disease.[8]

SUMMARY

The evidence adduced from the literature suggests, but does not establish, that as a result of peripheral nerve action alterations occur in the tissue supplied that either damage it or make it more susceptible to injury. Experiments were devised to test the validity of this thesis.

The model used in these experiments was the area of vasodilatation in the skin (flare zone) of the axone reflex, dependent as it is on the integrity of dorsal root fibers.

It is demonstrated that the pain threshold in the flare zone of the axone reflex is lowered during the process of spread of the flare.

It is also shown that this lowered pain threshold is a manifestation of increased tissue vulnerability, so that not only do previously non-noxious stimuli become noxious but mildly damaging stimuli become more damaging.

It follows from these experiments that the peripheral nervous system can further the disintegration of tissue it subserves. As such, by enhancing local inflammation it protects the whole organism at the cost of the integrity of a part.

‡ Brooks, C.: Personal communication to the author.

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MITRAL COMMISSUROTOMY

An Over-All Appraisal of Clinical and Hemodynamic Results

F. HENRY ELLIS Jr., M.D.
JOHN W. KIRKLIN, M.D.
ROBERT L. PARKER, M.D.
HOWARD B. BURCHELL, M.D.
AND
EARL H. WOOD, M.D.
ROCHESTER, MINN.

THE RELIEF of obstructing lesions of the mitral valve by mitral commissurotomy is now a widely accepted and extremely successful procedure. Sufficient time has elapsed since this procedure was first initiated to permit a valid appraisal of the over-all results. Although symptomatic results are important, the accumulation of objective data, when possible, adds greatly to our knowledge concerning the effect of an operative procedure. Such data are available in the form of hemodynamic studies carried out before operation, during operation, and at intervals after operation on patients undergoing mitral commissurotomy. We believe that the results of these hemodynamic studies present ample explanation for the marked symptomatic improvement that fully three quarters of these patients experience following operation.

OVER-ALL EXPERIENCE

We are presenting here our experience in 131 cases of mitral stenosis in which mitral commissurotomy was performed prior to April, 1954. Surgical incision of the commissures has been employed in addition to finger fracture in practically every case. The preoperative status of the patients, according to the classification of the New York Heart Association, is given in Table 1. As a general rule, patients without symptoms were not accepted for operation; hence, the two patients listed here in Group I are exceptions. One was an asymptomatic patient with a definite clinical diagnosis of mitral stenosis. Pregnancy was considered inadvisable because of her cardiac condition, and operation was undertaken because of her express desire to become pregnant. The other patient experienced episodes of paroxysmal nocturnal dyspnea but in the interim was entirely asymptomatic. As Table 1 shows, 24 patients were in Group II; 67 were in Group III, and 38 were in Group IV.

Read before the Section on Internal Medicine at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 22, 1954.

From the Mayo Clinic and Mayo Foundation: Section of Surgery (Drs. Ellis and Kirklin), Section of Medicine (Drs. Parker and Burchell), and Section of Physiology (Dr. Wood). The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Severely ill patients in Group IV are not denied operation even though the risk in this group may be high. This policy has been rewarding, in that many hopeless invalids have thereby been restored to a life of usefulness.

Eleven hospital deaths have occurred in the series of 131 patients, giving a mortality rate of 8.4% (Table 2). The increased risk of operation for patients in Group IV is apparent and is in agreement with the findings of others.* There were four deaths from cerebral emboli, one occurring on the operating table and the other three from two to seven days postoperatively. Three patients in Group IV died from 1 to 17 days postoperatively of progressive failure. One patient died the day following operation, of an unrecognized tension pneumothorax secondary to a ruptured subpleural bleb. One patient died 11 days after operation, of renal

TABLE 1.—*Mitral Stenosis: Preoperative Classification*

New York Heart Association Classification	Patients, No.
I	2
II	24
III	67
IV	38
Total	131

TABLE 2.—*Mitral Stenosis: Hospital Mortality for Mitral Commissurotomy*

New York Heart Association Classification	Patients Operated On, No.	Hospital Deaths	
		No.	%
I	2	0	0
II	24	0	0
III	67	3	4.5
IV	38	8	21.1
Total	131	11	8.4

shutdown. One patient in whom it was necessary to enter the left atrium via the left superior pulmonary vein died one month later, following thrombosis of that vein. One death occurred 40 days postoperatively, in a patient whose postoperative course was complicated by two episodes clinically suggestive of pulmonary embolism. Postmortem examination failed to reveal evidence of pulmonary emboli or to explain satisfactorily the cause of death.

CLINICAL RESULTS

The clinical results reported here are based on 94 traced patients operated on prior to January, 1954. The follow-up period varied from 3 months to 3 years, the average being 13.1 months. Most of these patients have been reexamined, while information from a few has been obtained only by letter. Three categories have been chosen into which postoperative patients surviving operation have been placed for purposes of evaluation. These are (1) excellent, (2) significant improvement,

*References 1 and 2.

and (3) failure. An operation is considered a failure if the patient does not improve, if the patient dies after returning home, or if significant disability from the residuals of a cerebral embolus remains.

To be considered as having an excellent result, a patient must be able to resume almost normal activities. A patient in Group IV, however, who postoperatively is classified in Group II is considered as having an excellent result. A patient who is in Group III preoperatively and who despite some improvement in exercise tolerance is only in Group II postoperatively is considered as showing significant improvement. Obviously, all patients who are in Group I postoperatively are classified as having an excellent result.

A total of 59 patients (62.8%) experienced an excellent result, while 23 patients (24.4%) were considered to be significantly improved. Thus, 87.2% of patients surviving operation received some benefit, while 12.8% (12 patients) represented

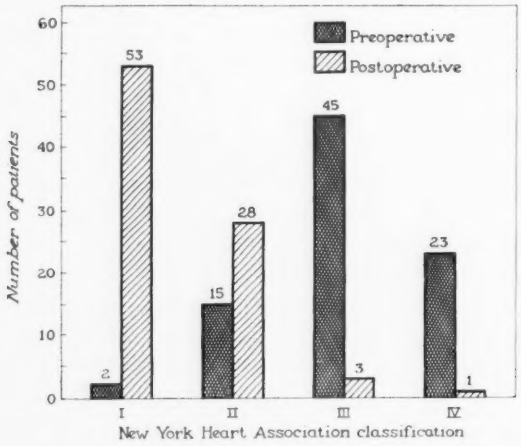

Fig. 1.—Preoperative and postoperative status of patients undergoing mitral commissurotomy. Only traced patients still living without significant residuals of cerebral embolism are included.

failures. When the 11 hospital deaths are included, operation was of benefit to 78.1% of the patients taken to operation, a figure comparable to those in other reported series.†

Figure 1 demonstrates the preoperative and postoperative status of 85 patients surviving mitral commissurotomy without significant residuals of cerebral embolism. Whereas only 17 patients were in Groups I and II preoperatively, 81 were in these two groups postoperatively. While 68 patients were in Groups III and IV preoperatively, only 4 were in these two groups postoperatively.

The postoperative results in four patients are worthy of special comment. These patients are represented in Table 3 and Figure 1 on the basis of the best postoperative status that they achieved. These four patients, however, subsequently experienced a recurrence of their preoperative symptoms after a period of six

† References 1 and 3-8.

months or more of significant improvement. The recurrence of symptoms was severe and disabling in two of these patients. Catheterization data obtained for one patient a year after operation showed abnormal findings of a degree identical to those found preoperatively; unfortunately, a study was not made three weeks after operation, but his very favorable clinical response for six months strongly suggests that a study at that time would have shown favorable changes. This patient died at the last admission, and necropsy showed healing of the commissurotomy incision. This case will be reported in detail subsequently. Because the clinical course in the other three patients has been similar to that of this case, in which so-called restenosis occurred, we believe that they fall into this category. Other examples of so-called restenosis following commissurotomy have been

TABLE 3.—*Mitral Stenosis: Clinical Results in Patients Surviving Mitral Commissurotomy**

Preoperative New York Heart Association Classification	Patients, No.	Result, No. of Patients				
				Failure		
		Excellent	Significant Improvement †	Late Death	Unimproved	Cerebral Residual
I	2	2	0	0	0	0
II	16	13	1	1	1	0
III	49	29	15	2	1	2
IV	27	15	7	4	1	0
Total	94	59 (62.8%)	23 (24.4%)	7	3	2

* All patients were followed for three months or more.
† Four patients in Groups III and IV showed evidence of significant improvement initially but later deteriorated functionally.

TABLE 4.—*Mitral Stenosis: Factors Influencing Results of Mitral Commissurotomy*

Factor	Patients *	Results					
		Excellent		Significant Improvement †		Failure ‡	
		No.	%	No.	%	No.	%
Pliable valve	61	44	72.1	13	21.3	4	6.6
Immobile valve	44	13	29.5	12	27.3	19	43.2
Preoperative regurgitation	23	5	21.7	8	34.8	10	43.5

* All cases included except untraced patients and patients operated on too recently for evaluation.
† Four patients with a pliable or immobile valve significantly improved initially but later deteriorated functionally.
‡ Includes hospital deaths.

reported.‡ We believe that before a patient should be so classified clinically he should demonstrate a definite and prolonged period (six months or more) of significant improvement followed by recurrence of symptoms.

FACTORS INVOLVED IN RESULTS

Many factors undoubtedly influence the results obtained following mitral commissurotomy. These include age of the patient, duration and severity of the disease, presence of associated valvular disease, history of previous systemic embolism, disturbance of cardiac rhythm, and completeness of the commissurotomy. One factor, however, which we consider of great importance is the anatomic status of the valve itself. In Table 4 the results are listed for patients with free pliable valves

‡ References 5 and 9-11.

and for those with valves which at the time of operation were in any degree immobile. This immobility varied from thickening of the valve to marked shortening and fusion of the chordae tendineae and actual valvular calcification. All patients, including those who died in the hospital, are included, except untraced patients and patients operated on too recently for evaluation. As may be seen, 57 of 61 patients with pliable valves (93.4%) were improved by the operation, while 25 of 44 patients with immobile valves (56.8%) were benefited. The operation was a failure in almost one half (43.2%) of the patients with immobile valves.

The presence of precommissurotomy regurgitation also was disadvantageous to the patient, failures occurring in almost one-half of such patients. This probably reflects more the presence of a scarred immobile valve than the regurgitation itself, for almost two-thirds of the patients with preoperative regurgitation had such a valve. There have been no early or late deaths due to surgically induced mitral regurgitation. On occasion, a slight amount of regurgitation has been produced surgically or regurgitation already present has been increased, but so far as we are aware the result in no patient has been affected thereby.

It has been suggested that mitral commissurotomy may fail to relieve the circulatory obstruction in certain patients with long-standing mitral stenosis, because of the presence of pulmonary vascular lesions which secondarily obstruct the pulmonic circulation.[12] However, pathologic study of the pulmonary vessels from specimens of lung removed at the time of mitral commissurotomy has been found to be unreliable in predicting whether or not a satisfactory functional response will result.§ Furthermore, we have been unable to find any clear correlation between the clinical response to commissurotomy and the level of preoperative pulmonary arteriolar resistance. Eighty per cent of patients who had a preoperative pulmonary arteriolar resistance of more than 500 dyne/sec./cm.$^{-5}$ were improved by mitral commissurotomy, while 87% of patients with levels of less than 500 dyne/sec./cm.$^{-5}$ were benefited by the operation.

HEMODYNAMIC EFFECTS OF MITRAL COMMISSUROTOMY

Although clinical data are important and, indeed, essential in the evaluation of a surgical procedure, objective data should be sought wherever possible, to verify clinical impression. There has been some difference of opinion regarding the hemodynamic changes that occur subsequent to commissurotomy, some stating that there is frequently little correlation between objective and clinical findings,‖ while others are of the opposite opinion.¶ We believe that quite definite hemodynamic changes occur after operation in those patients exhibiting clinical improvement.

We shall now review the hemodynamic changes recorded during operation and also those found at cardiac catheterization three weeks and one year after operation in certain of our 131 patients.

Hemodynamic Changes Occurring During Operation.—When pressures in the pulmonary artery and left atrium were recorded at the time of operation,[21] an

§ References 13 and 14.

‖ References 8, 10, 15, and 16.

¶ References 17-20.

immediate decrease in left atrial pressure to about one-half of the precommissurotomy value was noted in 20 of 21 patients (Fig. 2), and the mean pressure in the pulmonary artery dropped in 12 of 14 patients so studied.

These and other data obtained by Lev [21] in our laboratories allow several conclusions. In most patients with mitral stenosis for whom an adequate commissurotomy is done, there is an immediate fall in left atrial pressure. There is a concomitant fall of pressure in the pulmonary artery, which is of such degree as to be explained as a simple back-pressure result of reduction in left atrial pressure. The data showed no immediate reduction in pulmonary arteriolar resistance and no consistent immediate change in cardiac output.

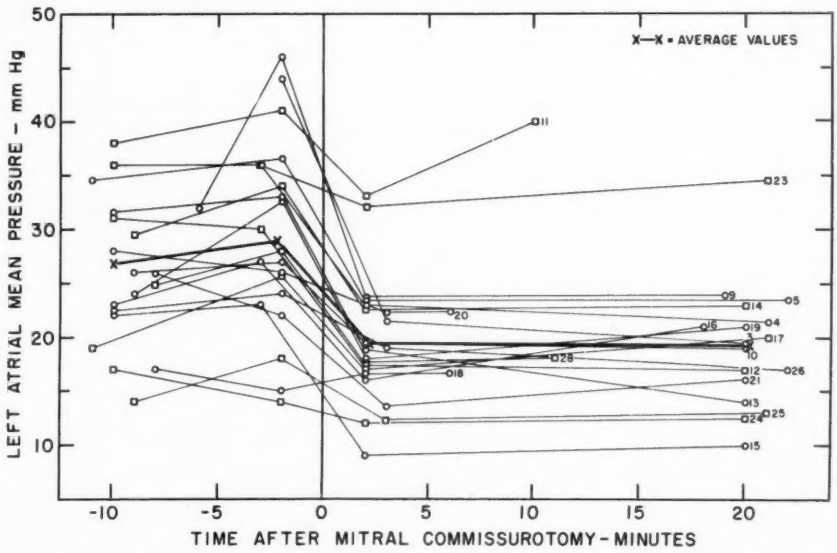

Fig. 2.—Changes in left atrial pressure during mitral commissurotomy in 21 patients with mitral stenosis. The data are plotted in relation to the time of commissurotomy, indicated by the central vertical line. Individual cases are indicated by a series of circles or squares joined by fine lines, and the average value for the group is indicated by the series of crosses joined by the heavy line. (The number following the terminal circle or square for each patient is the case number.) In 20 of the 21 cases, a decrease in mean pressure is evident. (Reproduced with permission from Lev, R.; Connolly, D. C.; Kirklin, J. W., and Wood, E. H.: The Immediate Hemodynamic Effects of Mitral Commissurotomy During Surgery, in Surgical Forum: Proceedings of the Forum Sessions, 39th Clinical Congress of the American College of Surgeons, Chicago, October, 1953, Philadelphia, W. B. Saunders Company, 1954, pp. 13-17.)

Changes Found at Early and Late Postoperative Cardiac Catheterization.—Tompkins and co-workers,# in our laboratories, have studied the physiologic findings in 12 of the patients reported on here, the data being obtained in each case at cardiac catheterization preoperatively, three weeks postoperatively, and approximately one year postoperatively. Only certain features of that study will be reviewed here, to demonstrate that objective changes in hemodynamics persist after successful commissurotomy.

Tompkins, R. G.; Wood, E. H.; Kirklin, J. W., and Burchell, H. B.: Unpublished data.

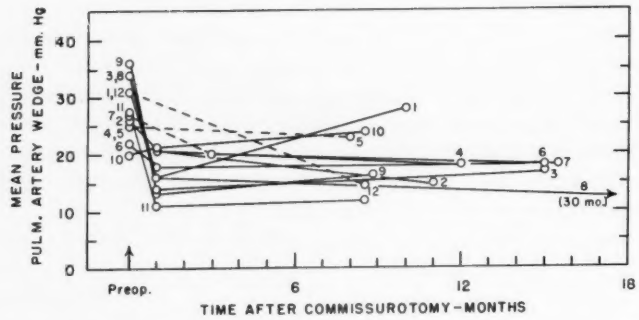

Fig. 3.—Changes in pulmonary-artery-wedge pressure at varying intervals after commissurotomy. A marked reduction in pressure was evident three weeks postoperatively, and this was still evident in all but one case at the late postoperative catheterization.

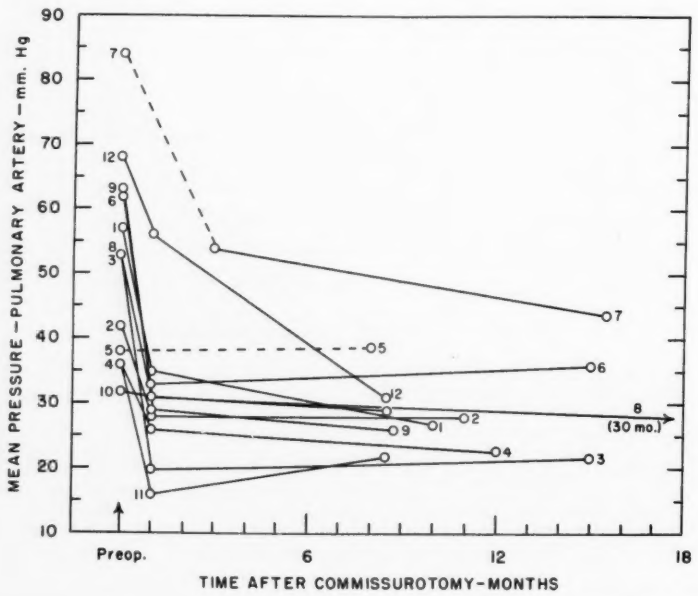

Fig. 4.—Changes in pulmonary-artery pressure at varying intervals after commissurotomy. A marked reduction in pressure was evident three weeks postoperatively, and this was still evident in most cases at the late postoperative catheterization.

In eight of nine cases in which data were available, the mean pulmonary-artery-wedge pressure three weeks after operation was strikingly lower than it had been preoperatively (Fig. 3). Even more significant is the fact that this reduction was still present in seven of these eight patients at the late postoperative catheterization. In one instance these studies were made two and one-half years after operation. A similar trend is apparent in the data on pressure changes in the pulmonary artery (Fig. 4). This indicates that the immediate reduction in left atrial pressure found at operation is maintained in most patients for the period in which they have been observed.

Pulmonary arteriolar resistance was found to be significantly reduced in most patients three weeks after operation, and this reduction either became greater or

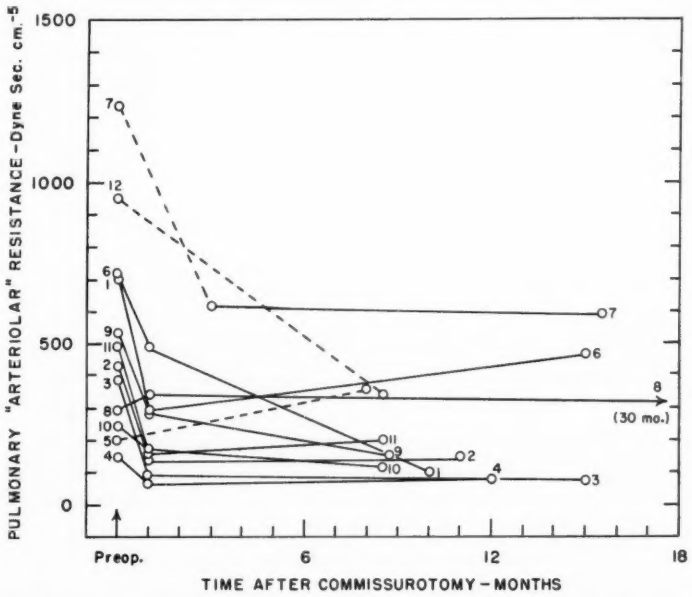

Fig. 5.—Changes in pulmonary arteriolar resistance at varying intervals after commissurotomy. A significant reduction in pressure occurred in most patients three weeks postoperatively, and this tended to persist, as was evident at the late postoperative catheterization.

stayed the same in the ensuing year in most patients (Fig. 5). This phenomenon was not an immediate result of commissurotomy, it is to be recalled. A lowering of the resistance imposed by the "arterioles" of the lung must, therefore, occur in the first three weeks after operation, reducing pressure in the pulmonary artery still further.

Although immediate changes in cardiac output in the operating room after commissurotomy were not found consistently by Lev and associates,[21] changes in the response of cardiac output to exercise were definite in the postoperative studies (Fig. 6). Preoperatively, most of the patients in this group increased their cardiac output little or none in response to a standard exercise test. All patients, save one,

studied three weeks postoperatively, were able to increase the cardiac output to a greater degree than preoperatively. Further, in seven cases a considerably greater increase in output was present at the time of the late postoperative study than was present three weeks after operation.

It happened that each of the 12 patients who was studied by Tompkins and associates * and in whom there was postoperative improvement in one or more physiologic variables either had an excellent result or was significantly improved. On the other hand, in two of the patients of the group classified as failures who were studied by cardiac catheterization preoperatively and three weeks postoperatively the postoperative physiologic variables showed no change from those

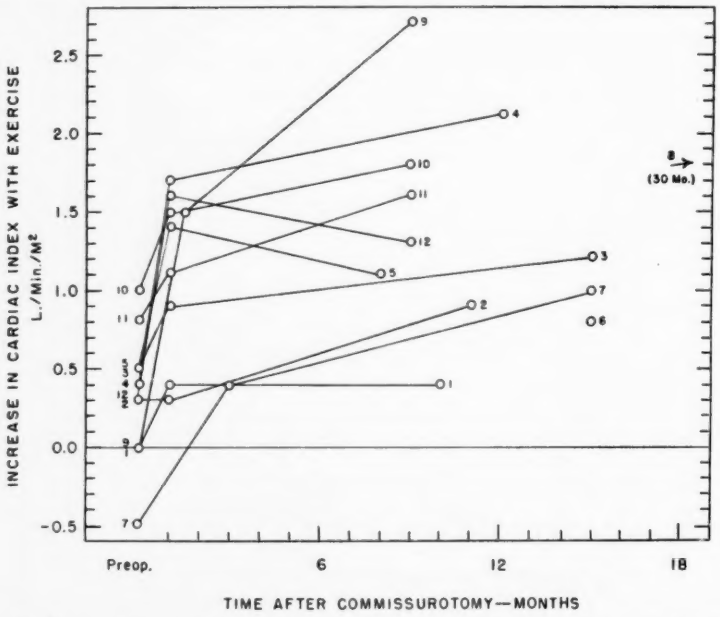

Fig. 6.—Changes in cardiac index on exercise at varying intervals after commissurotomy. A significant increase occurred in all but one patient three weeks postoperatively. A considerably greater increase was present in seven cases at the late postoperative catheterization.

recorded preoperatively. These are the only patients in whom no demonstrable changes in any of the physiologic variables were found at postoperative cardiac catheterization.

COMMENT

Postcommissurotomy changes for various physiologic data give objective evidence which corroborates the degree of functional improvement that these patients experience clinically. Two factors must be borne in mind in considering postoperative hemodynamic changes. In the first place, although an immediate fall occurs at operation in left atrial and pulmonary-artery pressure, no such dramatic change toward normal occurs in cardiac output or pulmonary arteriolar resistance. There

* Tompkins, R. G.; Wood, E. H.; Kirklin, J. W., and Burchell, H.B.: Unpublished data.

is more gradual return to normal of the latter two variables following operation, and improvement in respect to them may continue for many months postoperatively. Secondly, although normal values may be reached for certain physiologic variables following commissurotomy, this is by no means the general rule. A basic abnormality still remains after mitral commissurotomy; namely, a scarred valve that still has an orifice considerably smaller than normal. This orifice, however, is wide enough to permit most patients to lead an active life without difficulty. Its abnormality remains reflected, however, in many instances in the failure of the circulatory hemodynamics to return completely to normal.

SUMMARY AND CONCLUSIONS

This report concerns 131 patients with mitral stenosis who have undergone mitral commissurotomy. There were 11 hospital deaths, giving a mortality rate of 8.4%. Of the patients surviving operation, 87.2% either achieved an excellent result or were significantly improved.

A significant factor influencing postoperative results was the anatomic status of the mitral valve. In only 6.6% of patients with pliable valves was the operation a failure, while 43.2% of those with scarred, immobile, often calcified valves either died subsequent to operation or were unimproved.

Hemodynamic changes occurring during mitral commissurotomy include a decrease in left atrial and pulmonary artery pressure. Hemodynamic changes present three weeks after operation include a reduction in pulmonary-artery-wedge pressure, pulmonary-artery pressure, and pulmonary arteriolar resistance and an increase in the ability of patients to increase their cardiac index on exercise. These changes persist in most instances and may become more marked a year or more after operation.

The postcommissurotomy changes for various physiologic variables give objective evidence which corroborates the functional improvement that these patients experience clinically.

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NUTRITIONAL HEPATIC INJURY

HANS POPPER, M.D.
AND
FENTON SCHAFFNER, M.D.
CHICAGO

CLINICAL, functional, and structural alteration of the liver due to disturbances of nutrition have attracted increasing interest for many unrelated reasons. Changes were seen in frank starvation in concentration or prisoner-of-war camps,* in undernutrition, in disease, and in malnutrition resulting from poorly balanced therapeutic diets. Moreover, the role of malnutrition in the hepatic alterations of tropical disorders and alcoholism has been appreciated. Basically, three mechanisms produce nutritional injury: (*a*) undernutrition or starvation, (*b*) specific deficiency of one dietary constituent, and (*c*) imbalanced nutrition (malnutrition). The total caloric intake is not necessarily altered in the last two. From the practical point of view, at least in this country, undernutrition and specific deficiency are far less important than malnutrition. Clinical observations concerning nutritional hepatic injury are difficult to evaluate, because of the unreliability of the nutritional history and because of the frequent coincidence of other factors, especially infections. The study of the problem has received great impetus from animal experiments in which well-defined nutritional injuries were produced at will. The opportunity to combine observations of a large amount of autopsy material in a charity hospital in which examples of malnutrition are common with studies of different types of experimental malnutrition provided the incentive to survey the information available in various fields. The application of concepts developed in the study of animals as parallelisms for the understanding of human lesions necessitated deliberate oversimplification in a field in which knowledge is still sketchy.

The clinical material on which this correlation is based consists of 1,320 cases of cirrhosis observed among 31,869 autopsies from 1929 to 1954, 122 cases of cirrhosis studied by needle biopsy, and 686 autopsy cases and 19 biopsy specimens of severe fatty metamorphosis of the liver. The experimental studies, almost entirely conducted on rats, include the effect of high-protein low-fat diets alone and combined with toxins,† choline-deficient diets,[6] and the effect of acute and chronic administration of ethionine, an antagonist to methionine,‡ and of bromobenzene, which is supposed to drain sulfur amino acids from the liver.[8]

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From the Hektoen Institute for Medical Research and Departments of Pathology, Cook County Hospital and Northwestern University Medical School.

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* References 1-3.

† References 4-6.

‡ References 5 and 7.

STARVATION

Experimental starvation reduces the size of the liver and decreases cytoplasmic components, glycogen, protein, and nucleoprotein, by utilization of hepatic and body stores.[9] In some animals this is associated with fatty metamorphosis. In man the basic lesion in uncomplicated starvation is brown atrophy, as seen in debilitating diseases, senility, and carcinoma of the upper gastrointestinal tract. The liver loses more weight than any other organ in the body.§ The hepatic cells are considerably smaller than normal; the Kupffer cells are enlarged and both contain iron and wear-and-tear pigment.‖ Fatty and inflammatory changes, frequently seen, are probably the result of intercurrent infections. Only fragmentary data are available as to hepatic functional impairment in clinical starvation, although there is no clear-cut evidence for hepatic insufficiency.¶

SPECIFIC DEFICIENCIES

The best known deficiencies, the avitaminoses, have little effect on the liver. Hepatic changes, if any, are those of a nonspecific reaction to disorders elsewhere in the body. The most significant changes, at least in animals, occur in apparent specific deficiencies of protein, individual amino acids, and choline.

Protein Deficiency.—The effects of decreased intake or absorption of protein are similar to those of starvation. The stainable protein in the hepatic cells is reduced, and the basophilic cytoplasmic nucleoproteins supposedly related to protein formation disappear.# This is associated with a large number of chemical alterations, particularly with reduction of many hepatic enzymes * and a redistribution of intracellular components. The fat content generally increases but may disappear with prolonged protein depletion. In most experiments, reduction of dietary protein is associated with an increase of other nutrients, especially fat, and therefore this is malnutrition (imbalance) rather than deficiency.

Deficiency of Specific Amino Acids.—Deficiency of one essential amino acid is theoretically analogous to protein deficiency, since tissue protein formation is inhibited. However, fatty liver results from deficiency of various amino acids such as threonine, lysine,[17] tryptophan,[18] and leucine.[19] This also includes methionine,[20] which serves not only as an essential amino acid but as a sulfur and methyl donor. In contrast, deficiency of cystine, another sulfur donor, leads to hemorrhagic necrosis of the liver.† The specificity of these deficiencies is questionable, and they may in reality represent disturbances in a balanced system, as is established in the case of methionine.

Deficiency of Choline.—Fatty metamorphosis develops on diets nearly free of choline and also low in methionine.‡ It starts in the centrolobular zone and eventually results in large fatty cysts.§ Slight hyperbilirubinemia and sulfobromophthalein

§ References 2 and 10.
‖ References 1 and 2.
¶ References 3, 11, and 12.
# References 13 and 14.
* References 15 and 16.
† References 21 and 22.
‡ References 23 and 24.
§ References 25 and 26.

(Bromsulphalein) retention without other evidence of hepatocellular injury are present.[6] Later, connective tissue septums, starting in the lobular center, result in cirrhosis formation,[26] and eventually hepatic carcinoma develops.[27] The effects of choline deficiency are exaggerated in growing animals but can be largely prevented either by administration of methionine and other methyl providers or by starvation and administration of vitamin B_{12}, which spare methyl groups.‖ Therefore, although choline seems to be an essential nutrient, it is in reality also merely one part of a balanced system.

Conditioned Deficiencies.—Deficiency of various nutrients or body constituents may occur despite normal nutrition.[30] The availability to the liver of a substance may be reduced by processes within the body as well as by faulty intestinal absorption. Experimentally produced hepatic lesions illustrate patterns possibly occurring in clinical medicine. One example is the effect of ethionine, an analogue, and possibly the biologic antagonist, of methionine, with the methyl group replaced by ethyl. Ethionine reportedly interferes with protein synthesis in the liver [31] and with choline metabolism.[32] Single doses produce fatty liver in female rats but not in males.[33] After a transient stage of fatty liver (Fig. 1 *A*), prolonged administration produces hepatocellular degeneration and regeneration associated with interstitial infiltration, cholangiolar proliferation, and diffuse fibrosis (Fig. 1 *B*).[6] In rats kept alive by alternation between an ethionine-containing diet and a normal one a diffuse cirrhosis (Fig. 1 *C*) develops and hepatocellular or cholangiofibrotic (Fig. 1 *D*) tumors appear as they do on carcinogenic diets before frankly malignant lesions appear. Pancreatic degeneration, inflammation, and atrophy are found (Fig. 1 *E*).[34] Methionine given in excess of ethionine prevents or cures the lesion. Cortisone is protective, whereas conditions or substances that strain protein metabolism, such as pregnancy, are aggravating.[6] Animals with ethionine intoxication are very susceptible to bacterial infection. Although a toxic effect of ethionine cannot be entirely excluded, the fact that a methionine antagonist experimentally produces the gamut of hepatic lesions encountered in human malnutrition aids in the interpretation of the course of events of the latter.

Another pattern of conditioned sulfur amino deficiency is represented by the administration of bromobenzene, which is excreted in the urine coupled to cysteine as mercapturic acid.[35] The depletion of cysteine and its precursors, cystine and methionine, is associated with central hepatic necrosis, which can be prevented by methionine or cysteine.[8] The effects of other poisons, such as carbon tetrachloride, chloroform, or selenium, ameliorated by the administration of amino acids, especially methionine,¶ can also be interpreted as conditioned amino acid deficiencies, in which toxicity and deficiency become one.

NUTRITIONAL IMBALANCE IN ANIMAL EXPERIMENTS

The two most significant patterns in experimental nutritional hepatic injury are fatty liver and dietary massive necrosis. They were frequently produced together in the same animal and have been separated only recently.

Nutritional Fatty Liver.—The study of the fatty liver resulting from either choline or methionine deficiency led to the concept of lipotropic substances which

‖ References 28 and 29.

¶ References 36-38.

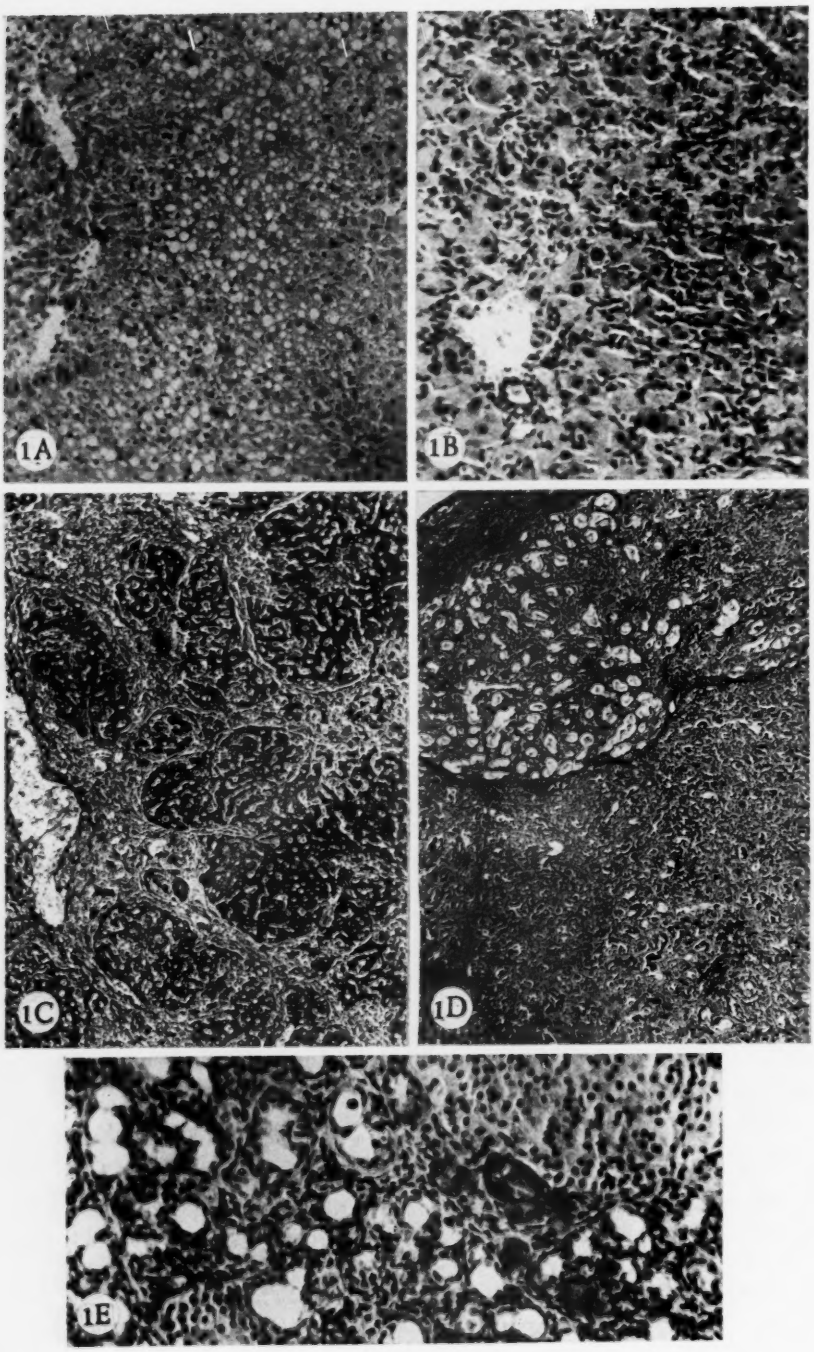

Figure 1

(See legends on opposite page)

are important in the removal of fat from the liver [39] (either by providing part of the phospholipid for serum transport [40] or by aiding in cellular fat oxidation [41]). Many of the lipotropes are able to replace each other almost completely,# and the need for them is determined by such factors as dietary fat, vitamin B_{12}, and folic acid intake [43] or by metabolic needs.[38] Hormones [44] and vitamins [29] determine the level of metabolic activity and therefore the demands for nutrients, although some hormones influence fat deposition directly.[45] Reduction of the total caloric intake reduces the need for lipotropes.[46] The interplay of these factors is represented by a balance between lipotropic and lipogenic factors (Fig. 2). They are best visualized as placed on a scale; if the pointer swings too much to the lipogenic side, fatty liver progresses to a diffuse cirrhosis. The analogy with the human fatty cirrhosis is apparent etiologically, despite morphologic differences. In the sense of this balance, increased fat intake, if accompanied by intake of sufficient biologically adequate protein, does not lead to fatty liver. Therapeutic dietary supplements are needed only if adequate protein intake is impossible or undesirable. Another way of looking at this balance is the consideration of the protein content as a percentage of the total caloric intake; reduction of this percentage may cause hepatic and pancreatic changes even though the absolute protein intake is still adequate. Since it is not established whether loading the balance with another lipotropic agent prevents or cures such changes, the oversimplification of such a balance should be stressed. Attempts to produce hepatic injury experimentally by alcohol excess have recently been successful, and the available evidence suggests that imbalance created by the increased calories from the alcohol results in insufficiency of lipotropic agents.*

Necrosis.—Diets deficient in cystine and vitamin E and a so-called third factor produce a sudden massive hepatic necrosis in rats after several weeks.† If this is not fatal, it may lead to postnecrotic scarring [53] or cirrhosis.‡ Adequate supply of any one of the factors prevents the lesion. Therefore, it appears that chemically and nutritionally heterogeneous factors are metabolically interrelated and that deficiency of any one may be regarded as imbalance. Antibiotics are modifying

References 38 and 42.

* References 47 and 48.

† References 21 and 49-52.

‡ References 51 and 52.

EXPLANATION OF FIGURE 1

Fig. 1.—Photomicrographs of various stages of ethionine intoxication in female rats, illustrating an example of conditioned amino acid deficiency. *A*, liver after administration of one dose of 100 mg. ethionine per 100 gm. body weight; diffuse fatty metamorphosis. Hematoxylin and eosin; × 90. *B*, liver after administration of a diet containing 0.5% ethionine for 35 days; diffuse hepatocellular degeneration and regeneration; interstitial infiltration; diffuse fibrosis. Hematoxylin and eosin; × 190. *C*, liver after administration of an 0.5% ethionine diet alternating with a stock diet for 192 days; cirrhosis formation; regenerative nodules are separated by connective tissue septums of various thicknesses. Mallory stain; × 62. *D*, liver after administration of an 0.5% ethionine diet alternating with a stock diet for 241 days; cholangiofibrotic nodules replacing the normal architecture. Hematoxylin and eosin; × 52. *E*, pancreas after administration of an 0.5% ethionine diet for 35 days; diffuse interstitial fibrosis, irregular degeneration and regeneration of acinar cells, and dilatation of ducts. Hematoxylin and eosin; × 240.

factors in retarding or preventing massive necrosis and, under certain circumstances, nutritional fatty liver.§ Substances which protect the liver against necrosis enhance the development of fatty metamorphosis and vice versa.[56]

HUMAN HEPATIC INJURY DUE TO MALNUTRITION

Controlled human experimental studies are few. Diets producing fatty livers in rats cause enlargement of the human liver, sulfobromophthalein retention, and abnormal blood lactate and pyruvate levels.[57] The disappearance of nutritional damage in alcoholics on experimental diets has been studied.[58] Mass experiences in tropical malnutrition (kwashiorkor) provide a partial substitute for controlled experiments.‖

Concepts derived from animal experiments such as lipotropic-lipogenic balance (with the effect of starvation), conditioned deficiency, and metabolically interre-

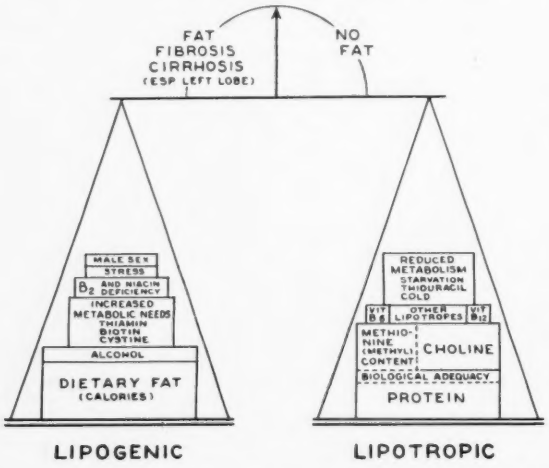

Fig. 2.—Balance between lipogenic and lipotropic substances, its disturbance leading to the fatty liver-cirrhosis syndrome.

lated heterogeneous factors, as well as the analysis of the morphogenetic processes leading to the fatty liver-cirrhosis syndrome, assist in the clarification of the problem of hepatic injury in human malnutrition. Some of the concepts are readily applied, whereas others may guide future thoughts.

Malnutrition in the sense of a disturbed lipotropic-lipogenic balance is the main cause of the human fatty liver-cirrhosis syndrome. A gradual transition can be observed from (1) an increase in central fat to (2) diffuse fatty metamorphosis to (3) the formation of fatty cysts (due to coalescence of fat-laden liver cells) to (4) increasing fibrosis and cirrhosis. Different stages of this arbitrarily divided process may be seen in the same liver. Some have maintained that the fatty metamorphosis as such causes cirrhosis,¶ whereas others have denied this.# In human tropical

§ References 54 and 55.
‖ References 59-61.
¶ References 24, 25, and 51.
# References 60, 62, and 63.

malnutrition [60] and in ethionine-intoxicated animals [6] a fat-free interval lies between the period of fatty metamorphosis and that of cirrhosis formation. The morphogenetic processes in this transition in man favor necrosis and variations of the fat content in different territories of the liver rather than permanency of the fatty metamorphosis.[64] Pancreatic degeneration with fat necrosis as well as chronic pancreatic fibrosis frequently accompanies and sometimes aggravates the condition.[65]

Fatty liver may be caused by toxic, anoxic, neurohormonal, or nutritional factors. The first three are seldom severe or persistent enough to produce the syndrome and are usually clinically insignificant complications of other conditions. The fatty liver of obesity, supposedly producing hyperglycemia and glycosuria, is a special example.[66] Malnutrition in the Temperate Zone is most commonly found in the chronic alcoholic, who consumes many calories in the form of alcohol without counterbalancing them with lipotropic nutrients, primarily protein. Furthermore, that which is eaten is not fully absorbed, owing to difficulties of intestinal absorption caused by associated gastrointestinal [67] and possibly pancreatic [65] dysfunction. The results of animal experiments and the response of patients to diet therapy shifted the emphasis from toxic to nutritional factors as the cause of the hepatic lesion in the alcoholic. The nutritional disturbances in primary gastrointestinal diseases, such as pancreatitis, colitis, and enteritis, may also initiate the syndrome, but these are far less frequent.

Tropical malnutrition is another widespread example of human nutritional hepatic injury, and the African tribal name of kwashiorkor has been associated with all the varied forms.[59] It consists of a fatty liver, often associated with cirrhosis, beginning in childhood, and in many areas primary carcinoma of the liver is common.* The underlying factors depend on local nutritional conditions, but basically they are either quantitative deficiency of protein or inadequacy of available protein in comparison to the usually high-calorie diet (mostly carbohydrates).[59]

Modifying Factors.—The fatty liver-cirrhosis syndrome is modified by various factors, most of which produce necrosis and are of importance in its progression. Infections, such as upper respiratory disease, pneumonia, pulmonary tuberculosis, and tuberculous peritonitis, aggravate the condition, sometimes catastrophically.† Malaria and other tropical diseases act similarly in kwashiorkor.[63] Hypoproteinemia probably results in lowered resistance to these diseases. Viral hepatitis is not a factor in alcoholism or tropical malnutrition, at least as judged anatomically. Toxic factors in alcoholic beverages [70] or elsewhere cause necrosis or vascular changes (e. g., bush tea in Jamaica [71]) perhaps similar to conditioned deficiencies. Anemia from bleeding varices or peptic ulcers, cardiac failure, or shock also produce necrosis. The recognition of all these factors is important, for they can be treated successfully with antibiotics, diet, blood, or surgery. Genetic factors may be important, although they are poorly understood.

Functional Significance of Fatty Liver and Cirrhosis.—The degree of fatty metamorphosis is poorly correlated with results of hepatic tests in both experimental animals and man.‡ The only exception is sulfobromophthalein retention, which in

* References 60 and 61.
† References 68 and 69.
‡ References 69 and 72-74.

this instance reflects disturbed circulation through the liver, probably as a result of mechanical obstruction rather than hepatocellular insufficiency. Abnormal results of other hepatic tests suggest associated hepatocellular degeneration.[75]

Cirrhosis is characterized by altered reconstruction of the lobular parenchyma with formation of (*a*) regenerative nodules, the arrangement of which is independent of preexisting lobules,[76] and (*b*) venous anastomoses between portal vein and hepatic artery branches and the tributaries of the hepatic vein.[77] The regenerative nodules exert pressure upon the hepatic veins, causing portal hypertension and its sequelae, splenomegaly and esophageal varices, and contribute to ascites formation. The portohepatic venous anastomoses interfere with the nutrition of the lobular and nodular parenchyma by shunting blood away from it. This produces hepatic necrosis, mainly central, and is another factor active in cirrhosis formation. The inflammatory changes reactive to necrosis within the lobule as well as within the septums indicate the activity of the process. Abnormal results of tests which mirror inflammation, such as elevation of gamma globulin or sedimentation rate, are found in most instances of cirrhosis even when other abnormalities suggesting hepatocellular injury (abnormal cephalin flocculation and thymol turbidity, lowered cholesterol esters, and urobilinogenuria) are not present.[75] The serum albumin is usually decreased in all stages of the fatty liver-cirrhosis syndrome. Evidence of disturbed bile flow (elevated serum bilirubin, alkaline phosphatase, and total cholesterol and bilirubinuria) need not be present. Clinically, every case of cirrhosis, including the nutritional variety, must be evaluated from three points of view: (1) the degree of liver cell damage, which is often related to the degree of jaundice, if jaundice is present; (2) the rate of progression of the cirrhotic process, which is reflected mainly in the inflammatory and connective tissue changes as an indication of the rate of destruction of the lobular architecture, and (3) the extent to which the cirrhotic process has advanced. For example, in advanced "atrophic" cirrhosis, at the time of observation, no evidence of hepatic failure or jaundice or activity may be found.

CLINICOPATHOLOGICAL ENTITIES

Simple Nutritional Fatty Liver.—Over 70% of alcoholics with enlarged livers have fatty metamorphosis proved by biopsy.[78] Splenomegaly is rarely found, but ascites, edema, or spider nevi do occur. Slight jaundice is occasionally present, and the accompanying vitamin deficiencies account for the frequently noted peripheral neuritis and glossitis. Sudden death without obvious explanation has been related to glycogen exhaustion of the liver. The commonest functional abnormality is sulfobromophthalein retention.§ Serum albumin is often reduced. Cephalin flocculation and serum alkaline phosphatase are increased in about a third of the cases, whereas thymol turbidity is abnormal in only 20%.

At autopsy the liver is greatly enlarged, and, histologically, severe fatty metamorphosis gives sections a Swiss-cheese appearance. There are some areas of focal necrosis, and the portal triads are infiltrated with round cells (Fig. 3*A*). Connective tissue membranes extend from the central and peripheral areas. Infections, especially lobar pneumonia, are frequent causes of death. They are treacherous in such patients, because fever and other systemic manifestations may be suppressed or overlooked, so that the patient consults the physician late. Intracellular fat dis-

§ References 69, 72-74, 78, and 79.

appears in three weeks under therapy, whereas fat in cysts is usually gone within six weeks.|| Continued alcohol abuse and poor dietary intake maintain the fat. There is little evidence that choline supplements improve the effect of a nutritious diet.¶

Fatty Liver with Acute Hepatic Failure and Jaundice.—Sometimes in patients with nutritional fatty liver acute episodes of hepatic failure with jaundice may occur, often preceded by a period of reduced protein intake.# In many instances infections (influenza, pneumonia, tuberculosis) usher in the acute episode.* Jaundice may be mild or severe. In contrast to cirrhosis, the duration of symptoms, often referable to the gastrointestinal tract, is shorter; the patients are younger, and there is no male sex predominance.[64] Edema and ascites develop rapidly, especially in fatal cases. The mortality rate varies, depending on the material available, but may

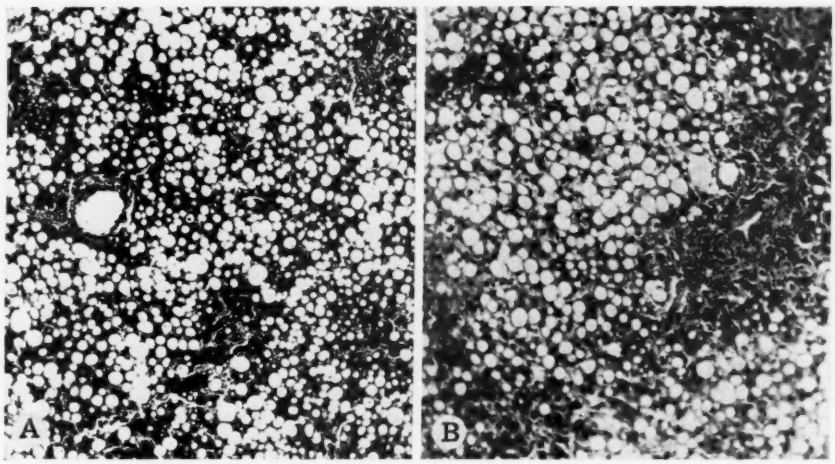

Fig. 3.—Stages of human fatty liver-cirrhosis syndrome. *A*, simple nutritional fatty liver. Mallory's aniline blue stain; × 58⅓. *B*, fatty liver with acute hepatic failure and jaundice; focal necroses and portal inflammation as well as bile stasis. Hematoxylin and eosin; × 75.

reach 20%, death usually being preceded by hepatic coma. The results of hepatic tests are abnormal, but in some cases cephalin flocculation and thymol turbidity are normal, whereas serum alkaline phosphatase is elevated, suggesting obstructive jaundice.† Histologically, focal necrosis and sometimes central necrosis is seen, and connective tissue septums may extend into the lobular parenchyma (Fig. 3 *B*).‡ Cirrhosis formation with its sequelae (portal hypertension), however, has not yet begun and cannot explain the acute fatality, which probably results from inability of the fatty liver to cope with the toxic effects of the infection.

|| References 69 and 80.
¶ References 69, 72, and 80.
# References 81 and 82.
* References 69 and 82.
† References 69 and 82.
‡ References 69, 78, 79, 81, and 83.

Rapid Transition of Fatty Liver into Cirrhosis (Florid Cirrhosis, Chronic Toxic Hepatitis).—In patients with a history of malnutrition, especially chronic alcoholism, an illness of six months' duration or more develops, with symptoms referable to the liver and gastrointestinal tract. Hepatic coma may develop with or without jaundice and is usually associated with uremia. The liver is large and

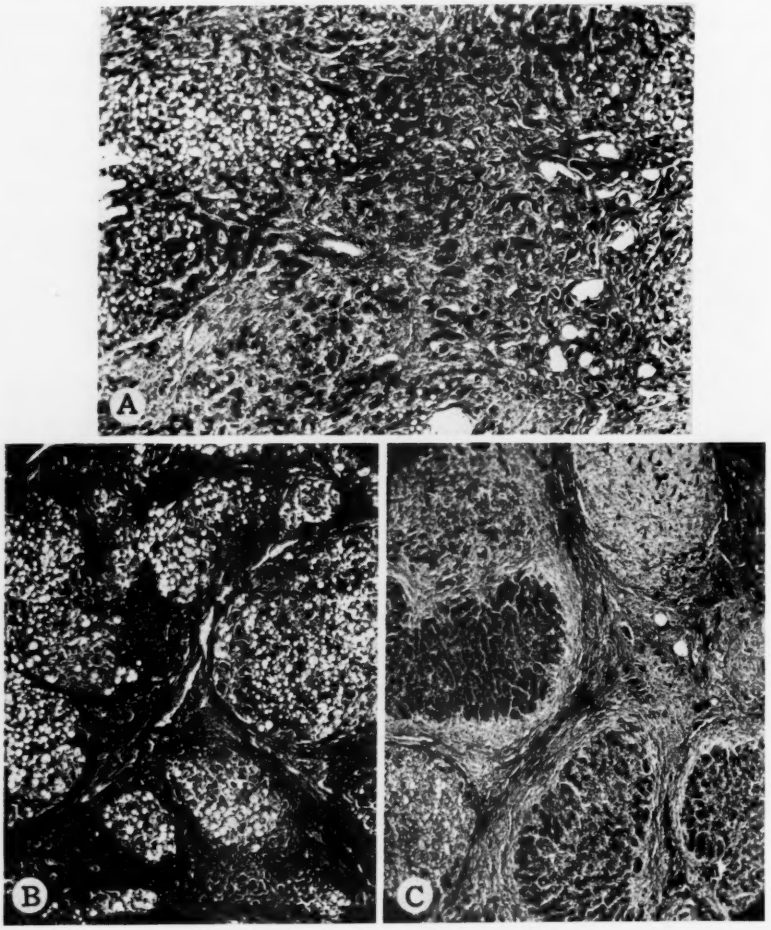

Fig. 4.—Stages of human fatty liver-cirrhosis syndrome. Mallory's aniline blue stain. *A*, rapid transition of fatty liver into cirrhosis (florid cirrhosis); hepatocellular degeneration, with focal regeneration and fatty metamorphosis; periportal inflammation; diffuse proliferation of collagenous membranes condensing to septums; × 58. *B*, fatty (septal) cirrhosis; transformation of the lobular into nodular architecture, the nodules containing fat; × 45½. *C*, Laennec's cirrhosis; nodules of similar size, some fat-containing, others fat-free, are separated by septums of various thicknesses; × 45½.

tender, and ascites may be present although splenomegaly is unusual. The results of hepatic tests indicate liver cell degeneration. At autopsy the lobular architecture of the slightly enlarged liver is obscured and the surface is smooth or finely granu-

lar. Histologically, hepatocellular degeneration with focal regeneration, patchy fatty metamorphosis, and cholangiolar proliferation are combined with proliferation of the Kupffer cells, periportal and portal inflammation, and a sprinkling of segmented leucocytes. This polymorphic picture of a hepatitis is distinctly different from viral hepatitis. In fatal cases, there may be central and submassive necrosis with collapse. Connective tissue membranes proliferate throughout, and septums traverse the lobule (Fig. 4*A*). Portohepatic venous anastomoses and a few regenerative nodules are found. The fat content of the liver is often low, probably as the result of treatment or starvation. Various nonhepatic infections, particularly tuberculosis, are noted. This is considered to be the cause of the chronic hepatic damage, to which the fatty liver is more susceptible. The lesion is thus rapidly advancing toward but is not yet diffuse fatty (septal) cirrhosis.

Fatty (Septal) Cirrhosis.—Eventually, connective tissue septums, starting in in the center, periphery, or anywhere else within the lobule subdivide it to a degree that nodules of various sizes form. These nodules grow and give the large or

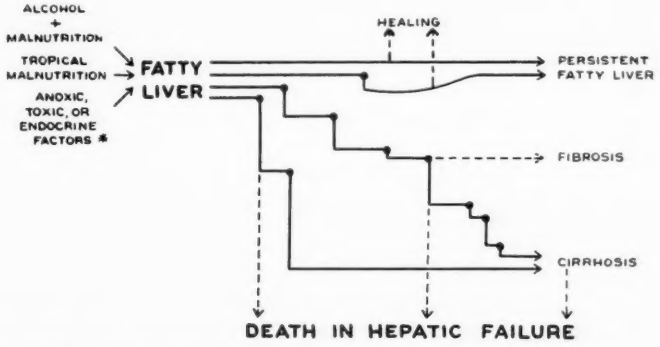

Fig. 5.—Course of the fatty liver-cirrhosis syndrome. Black dots indicate episodes of hepatic necrosis, sometimes preceded by infection elsewhere. The factors marked with an asterisk are usually not protracted enough to produce clinically significant fatty liver.

normal-sized liver a granular or nodular surface.§ Fat is found in varying amounts, depending on previous nutrition (Fig. 4*B*). The activity of the cirrhotic process itself and the degree of liver cell damage varies, the latter depending on intercurrent infection, toxic agents, or the cirrhotic alteration of the circulation. The degree of jaundice as well as the result of hepatic tests also varies. Spider nevi and portal hypertension with splenomegaly and esophageal varices are present in almost every instance. Death in this stage is usually due to hepatic failure or to hemorrhage from esophageal varices.

Laennec's Cirrhosis.—When fat has almost disappeared and the liver shrinks, it is no longer possible to recognize clinically, functionally, or anatomically the nutritional etiology that led to the cirrhosis.|| The nodular transformation is usually far advanced (Fig. 4*C*), but in some instances a burning out of the cirrhotic

§ References 83 and 84.

|| References 68, 75, 85, and 86.

process in an earlier stage may also leave remnants that fail to reveal the pathway of their development. Furthermore, fat may appear in livers which have become cirrhotic from other causes, as a result of associated malnutrition.¶ The laboratory findings in this stage do not vary from those of the diffuse fatty cirrhosis, but the term Laennec's cirrhosis, somewhat analogous to Bright's disease, is proposed for the condition, to designate a common terminal pathway of the multiple etiologic factors causing cirrhosis.

SUMMARY

The attempt has been made to utilize concepts developed from experiments in nutritional hepatic injury, such as the lipogenic-lipotropic balance, conditioned deficiency, modifying factors, and the effects of starvation in the study of human nutritional hepatic injury. In view of the usually poor dietary history given by most patients, these experimental observations provide a sounder basis for classification of human lesions. It appears that caloric undernutrition (starvation) and deficiencies of individual food constituents are less important than dietary imbalance, or malnutrition. The main result of malnutrition is the fatty liver-cirrhosis syndrome, predominantly encountered in alcoholics in the Temperate Zone (Fig. 5). The modification of the syndrome by such factors as intercurrent infection or toxins accounts for the variety of clinical manifestations and, quite likely, for the transition of the simple fatty liver into hepatic insufficiency and cirrhosis formation.

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Treatment in Internal Medicine

TREATMENT OF SICKLE CELL ANEMIA

BYRD S. LEAVELL, M.D.
CHARLOTTESVILLE, VA.

SICKLE cell anemia was described first by Herrick in 1910.[1] Since then, surveys of Negroes in the United States have revealed the incidence of the symptomless sickle cell trait to be about 9% and incidence of sickle cell anemia to be about 2.25 per thousand.[2] In the past decade sickle cell anemia has been the subject of many studies, which have contributed greatly to our understanding of many of the abnormalities that occur in the disease. Conclusions drawn from these studies form the basis for our current ideas of the pathogenesis of the disease. Since our present therapy is directed toward this aspect of the disease, the pathogenesis of sickle cell anemia will be reviewed briefly before treatment is discussed.

It now seems well established that the sickling phenomenon is due to a gene which produces sickle cell anemia when it is present in the homozygous state and sickle cell trait when it occurs in the heterozygous state.* The erythrocytes in both conditions are abnormal and assume the characteristic "sickle shape" when the hemoglobin is in the reduced form.[5] This characteristic of the cells has been shown to be due to hemoglobin that is different from the normal electrophoretically.† Erythrocytes in patients with sickle cell anemia contain only the abnormal "sickle cell" hemoglobin, while those of persons with the sickle cell trait contain a mixture of the abnormal "sickle cell" hemoglobin and normal hemoglobin. Studies of erythrocyte survival in vivo indicate that the increased hemolysis in sickle cell anemia is due to a defect in the erythrocytes, which have a survival time much shorter than normal, in contrast with those in sickle cell trait, which apparently have a normal life span.‡ A hemolytic type of anemia occurs because hematopoiesis, although increased, is not able to compensate for the excessive erythrocyte destruction. In many patients hemoglobin and erythrocyte levels remain essentially the same over a period of years because the life span of the red cells and the maximum compensatory effort that the bone marrow is able to make remain unchanged.§ On occasions this balance is upset, and the anemia rapidly becomes much more severe, either as a result of increased hemolysis or as a consequence of the development of a temporary aplastic state in the bone marrow.[15] Aside from the sickling property of the erythrocytes and the presence of anemia, probably the most characteristic feature of sickle cell anemia is the occurrence of sudden attacks of pain or other localized manifestations in almost any part of the body. These episodes appear to be explained by the capillary engorgement and areas of infarction that are found

From the Department of Internal Medicine, School of Medicine, University of Virginia Hospital; Professor of Internal Medicine.

* References 3 and 4.

† References 6 and 7.

‡ References 8-11.

§ References 12-14.

in the various organs at autopsy.[16] Some areas of infarction seen at autopsy are not accompanied by demonstrable thrombosis, and it has been postulated that vasospasm and packing of the vessels by distorted erythrocytes rather than thrombosis is responsible for the ischemic infarcts.[17] A possible explanation for this occurrence in sickle cell anemia and its absence in sickle cell trait has been given by the demonstration that the erythrocytes in sickle cell anemia assume the sickle form under conditions of higher oxygen tension than do those in sickle cell trait. The reported observations suggest that a reduction of oxygen tension sufficient to produce sickling and increased viscosity may occur in vivo in sickle cell anemia.[18] The same studies indicate that it is unlikely that oxygen tension of venous blood would be reduced enough to produce sickling in vivo in a person with sickle cell trait. Although the exact mechanism of the destruction of erythrocytes and the cause of the episodes of crisis are not known with certainty, the studies to date indicate that most of the clinical features of sickle cell anemia can be explained by the anemia per se and by the presence of erythrocytes that assume the sickle form in the circulation.

Correction of the anemia and the reduction of the in vivo sickling and blood viscosity have been attempted by numerous methods. These have been described in detailed reviews of the disease,‖ and not all will be mentioned here. Opinions on therapy sometimes differ as to the measures that should be employed and the indications for their use. This difference probably is due in large part to the difficulty of evaluating nonspecific treatment in a disease whose clinical course varies as widely as does that of sickle cell anemia.

Transfusion is one of the oldest and most widely used forms of treatment. The dangers associated with its use, such as hemolytic reaction, viral hepatitis, and hemosiderosis, are well known. Although it has not been our experience, reactions are said to be more frequent and more severe than usual in sickle cell anemia.¶ Another hazard to transfusion in this disease is the presence of heart failure in association with severe anemia. For these reasons transfusions should be used only when there is a definite indication. However, multiple transfusions will correct the anemia, because the normal erythrocytes transfused into a patient with sickle cell anemia survive for the normal time. Transfusions also produce other desirable results that are not always considered. As the sickle cell erythrocytes survive only a few weeks, multiple transfusions not only correct the anemia but also markedly reduce the number and concentration of sickle cell erythrocytes in the circulation, because the transfusions depress hemopoiesis and the production of sickle cells in the recipient. As a result, the patient's blood can be rendered essentially normal for a period of at least several weeks by the use of multiple transfusions.[23] Quicker results may be obtained by a modified exchange transfusion method, which is more suitable for children than for adults.[2]

The place of splenectomy in the treatment of this disease remains controversial. There is agreement that splenectomy is not a procedure that should be applied to all patients with sickle cell anemia, because the operation does not cure the hemolytic process and does not affect the sickling phenomenon. Furthermore, virtual "autosplenectomy" has been found at autopsy in some patients who suffered from

‖ References 2 and 19.

¶ References 20-22.

a severe form of the disease before death. Consideration of the procedure is limited to children and adults whose spleens are moderately or greatly enlarged. Our experience and a review of the reports of others indicate that most of the patients whose spleens extend to the umbilicus or below are greatly benefited by splenectomy.# The reason for the improvement is not clear. It is possible that the operation serves to remove the added hemolytic effect of "hypersplenism," which is similar to that found in many disorders associated with enlarged spleens, such as congestive splenomegaly, lymphoma, and some chronic infections. It is also possible that the most marked splenomegaly occurs in patients who have a milder disease, such as sickle cell trait-hemoglobin C combination rather than true sickle cell anemia.[34]

The anemia of sickle cell anemia rarely responds to anything but transfusion, and as a result the average patient with sickle cell anemia receives no treatment most of the time. The patient remains somewhat handicapped but not ill. The hemoglobin and red cell count remain stable, sometimes for a period of years. Treatment of the anemia with vitamin B_{12} and liver extract are ineffective, as would be expected. Iron is contraindicated, since the anemia may promote iron absorption and increase iron in the body tissues without any increase in iron utilization. Other measures that are useful in some hematological conditions have been tried in sickle cell anemia. The use of corticotropin (ACTH) in one patient was followed by a rise in erythrocytes to normal, a decrease in sickling, and a return of osmotic and mechanical fragility to normal.[25] Subsequent reports have suggested a possible use of cortisone and corticotropin in crisis[26] and in the treatment of leg ulcers.[27] The precipitation of crisis by corticotropin and cortisone has also been noted.* Because of these conflicting results, further studies of these drugs are necessary before they can be evaluated. The somewhat surprising report that cobalt chloride produced hematologic improvement in four patients with sickle cell anemia also needs further investigation.[28]

Some of the clinical manifestations of the disease, such as congestive heart failure, cerebral vascular accident, urinary tract hemorrhage, and priapism, are not peculiar to sickle cell anemia and are treated as they are when they occur in other circumstances. Other features of sickle cell anemia may require special measures. In some patients leg ulcers heal with the local application of antibiotics, but the more troublesome ulcers require bed rest and transfusions. Anesthesia, surgery, and pregnancy carry greater risk for the patient with sickle cell anemia than for the normal person and require special consideration.† As the increased risk is probably related to the anemia and to vascular accidents secondary to the sickling of the erythrocytes in the circulation, multiple transfusions prior to anesthesia or delivery seem worthy of trial, because both the anemia and the sicklemia can be virtually abolished within a week or two by this means.[23]

The occurrence of a severe episode of "crisis" is a serious development for the patient with sickle cell anemia. Although the patients usually recover from these episodes, death from sickle cell anemia in childhood and early adult life usually comes in an episode of "crisis" or during some intercurrent infection. At such times the patient may appear critically ill, with severe anemia, shock, and abdominal pain.

References 2 and 24.
* References 19 and 25.
† References 2, 19, and 29-31.

If severe anemia is present, oxygen and transfusions of whole blood or packed cells are indicated. The oxygen should not be continued over a long period, because it has been shown to depress marrow function.[32] Episodes of "crisis" often follow infection or fever, and for this reason infection should be searched for in various parts of the body and should be treated if possible. Surgical consultation and sound judgment are often necessary in patients with abdominal pain, for patients with sickle cell anemia may have the same surgical emergencies as other patients, and it should not be assumed that the pains are necessarily manifestations of the sickle cell disease. Relief of the abdominal pain and back pain may be very difficult. Mild sedation and analgesics may suffice for the milder back and abdominal pains, but even narcotics may fail to relieve the excruciating pain that some patients experience. Recently benzazoline (Priscoline) was reported to give dramatic relief of pain in seven children with sickle cell anemia, and this drug warrants further study.[33]

At present the treatment of sickle cell anemia is neither specific nor curative and leaves much to be desired. It is hoped that continued progress in our knowledge of the disease will lead to more satisfactory therapy. In the meantime, judicious use of methods now available can contribute to the comfort and survival of the unfortunate persons who are afflicted with this disease.

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Progress in Internal Medicine

SURVEY OF THE 1953 HEMATOLOGY LITERATURE

CLAUDE-STARR WRIGHT, M.D.
D. SHELTON MABRY, M.S.
RICHARD D. CARR, M.D.
AND
ANNA MAE PERRY, B.S.
COLUMBUS, OHIO

(Continued from page 678)

RED BLOOD CELLS

Production and General Observations on Erythrocyte Metabolism

A most comprehensive review and study of reticulocytes and a method for determining erythrocyte production have been presented by Seip.[324] Reference to the original monograph is recommended. Factors involved in the transmission of young red cells from the bone marrow to the blood are the oxygen concentration in the blood-regulating center of the hypothalamic region and a neurohumeral mechanism.[324] Reticulocytosis has been produced in rabbits and monkeys by intravenous administration of homologous anemic serum † and in humans by erythroblastotic sera.[324] A macronormoblastic erythropoiesis occurs in cardiac insufficiency.[327] A conditioned reflex for erythroid cell production was produced in rabbits by LoMonaco by exposure to simultaneous barometric depression and luminous stimuli daily. After 14 days of treatment, an increase of erythrocytes was induced by stimulation with light.[328]

Proliferation activity of the primitive erythroblast in the chick embryo is not synchronous but is governed by the law of fluctuating variability.[329] In bone marrow cultures from cases of chronic glomerulonephritis with anemia and azotemia, erythroblasts in homologous medium show diminished proliferation and maturation, while those in heterologous medium show normal values.[330] Hypophysectomy in rats induces an anemia simulated by removal of both the thyroid and adrenal glands.[331]

The distribution of lipids, polysaccharides, nucleic acids, and phosphatases in the normal human erythrocyte and other formed elements is reviewed, and cytochemical and microchemical methods are surveyed.‡

Studies of erythrocyte metabolism by use of C^{14}-tagged glucose show a high turnover rate in phosphoglycerates and emphasize the lack of protein and fat synthesis.§ Acetate is largely incorporated into the carbohydrate and lipid fractions of erythrocyte stroma.[336] Glutathione may be produced in the mature erythrocyte by enzymes derived from immature red cells or may be synthesized elsewhere.[337]

† References 325 and 326.
‡ References 332 and 333.
§ References 334 and 335.

Cytoplasmic nucleic acid concentrations of chicken bone marrow are lowest in reticulum-like cells and highest in the erythroblasts.[338] Structural proteins of chicken erythrocyte nuclei have been separated into three fractions by digestion and extraction.[339]

Plasma potassium concentration tends to increase with the age of the person; however, age does not affect erythrocyte potassium concentrations.[340] Erythrocytes from patients with diabetic acidosis have diminished sodium and potassium concentrations with normal water content.[341] Replacement of potassium seems to depend on the presence of an active cholinesterase and its substrate.[342] The Q-T interval in electrocardiograms follows the erythrocyte potassium concentration, while the height of the T waves follows the serum potassium concentration.[343] Potassium exchange rates have been studied in dogs under varying experimental conditions.[344] The effect of sodium fluoride on potassium exchange rates is dependent on inhibition of enzymic processes rather than on changes in membrane permeability.[345]

Cytochrome oxidase levels seem to be the limiting factor in regulating the respiratory rates of nucleated and non-nucleated erythrocytes.[346] Further study has been made of the inverse relationship of acetylcholinesterase activity of red cells and thrombocytes.[347] An enzyme present in the erythrocytes of man, dog, rabbit, and rat oxidizes thiocyanate to cyanide.[348] Three proteolytic enzymes have been extracted from human red cells.[349]

X-ray diffraction studies show random orientation and position of intracellular hemoglobin of normal or crenated erythrocytes.[350] Attempts to prepare red cell stroma free of iron and/or hemoglobin have not been successful.[351] Red cell ultrastructures (examined by electron microscopy) from patients with acquired and hereditary anemias, chronic leukemia, and polycythemia vera show various modifications, such as increased coarseness and hole and fold formation. Modification of normal cells with fixatives, salts of heavy metals, lowered pH, sensitization, and trypsinization also produced folding of the ultrastructure.[352]

Recent work on the problems of hemoglobin metabolism has been reviewed.‖ The rate of hemoglobin synthesis by water fleas varies directly with increases in temperature and iron concentration.[355] Hemoglobin levels decrease significantly with advancing age; men show less decrease than women. Men living alone have significantly lower hemoglobin levels than those living with their wives.[356]

The human fetus at term has 14.8 gm. of hemoglobin and 4,000,000 red cells unless excess production of cells is stimulated by oxygen lack.[357] The size of the erythrocyte in the child is the result of the hemoglobin which is available to an erythrocyte formation potential, specific to the age. The erythrocyte-forming capacity is more adequate than the hemoglobin-synthesizing capacity of the infant bone marrow.[358] Iron metabolism (page 818), fetal hemoglobin (page 825), and pathologic hemoglobin complexes (page 825), are discussed under their respective sections.

Erythrocyte Sedimentation Rate.—This nonspecific test is dependent on rouleaux formation, mediated by plasma/cell ratio and fibrinogen, globulin, and albumin levels of the blood.¶ Sources of variations in sedimentation determinations are

‖ References 353 and 354.

¶ References 298 and 359.

discussed in relation to physiological, pathophysiological, and technical factors.# It is claimed that the Westergren method gives results more consistent with the clinical status of the patient than does the Wintrobe method.[362] However, studies in children indicate so close a correlation between the Wintrobe, Westergren, and Landau-Adams determinations that all these methods are satisfactory.[365]

The type of anticoagulant used makes little difference, provided that the test is initiated within an hour after the sample is drawn.[365] Dilution with plasma to normal hemoglobin values is recommended for polycythemic bloods.[363]

The erythrocyte sedimentation rate is increased during pregnancy from the 5th to the 36th weeks. This rise is independent of age, parity, multiple pregnancy, or any of the common complications of pregnancy. The erythrocyte sedimentation rate is of no value as a diagnostic test of pregnancy or of infection during pregnancy.[298] Acute congestive heart failure usually produces elevated values, which persist after recovery, as does chronic cardiac insufficiency, except when the patient is succumbing to heart failure.[366] No differences are seen in patients with arteriosclerotic radio-opaque calcifications in the thoracic aorta.[367]

Increase in sedimentation rates observed in erythrocyte-oxypolygelatin systems results from pseudoagglutination of cells. This red cell aggregation can be reversed by the addition of sodium salicylate,[368] which has no effect on the sedimentation rate of freshly drawn blood.[369] Dextran sulfates of high molecular weight cause platelet and white cell agglutination and variable effects on the erythrocyte sedimentation rate.[370]

Blood Collection, Storage, Substitutes, Transfusions, and Volume

Storage and Preservation.—Blood storage methods have been reviewed.[371] The use of disodium ethylenediamine tetraacetate (Sequestrene), an anticoagulant, in place of citrate results in good post-transfusion survival of erythrocytes.[372] Use of 2 M glycerin in 0.12 M NaCl permits erythrocytes to be frozen as slowly as desired without damage.[373] About 98% of cells stored at —20 C. in 30% glycerin and 3% trisodium citrate remain nonhemolyzed for three months, and an estimated 90% can be recovered at the end of a year.[374] Other workers report over 90% recovery after storage at —70 C. for periods up to six and one-fourth months.[375] In order to facilitate the removal of glycerin, apparatus has been developed which has given 95% recovery of cells in early tests. The apparatus, based on the principle of a "long traverse centrifuge," removes glycerin from stored erythrocytes by continuous washing.[376]

Enhanced osmotic fragility of erythrocytes is retarded by 10-(2-dimethylamino-1-propyl) phenothiazine (promethazine; Phenergan). Although morphologic preservation is increased, this method has not yet been shown to prolong the useful shelf-life of stored blood.[377]

Concentrated red cell transfusions are frequently preferable to whole blood in many anemic patients requiring transfusions. Of course, whole blood is preferred in the treatment of shock or hemorrhage, where the blood volume is low. The transfusion reaction rate (2.9%) for packed cells is slightly less than that for citrated blood controls.[378]

References 359-364.

Chemical and hematologic changes occurring in plastic bags for blood storage are similar to, but slower than, those occurring in glass containers.[379] In another study, Wall and co-workers have compared in vitro and in vivo behavior of blood stored in plastic and glass containers. Erythrocytes stored in glass exhibit better survival times than those stored in plastic. Again it was shown that in vitro studies do not correlate with in vivo results.*

Developments of atraumatic centrifuge equipment allows the separation of reasonably normal leucocytes and platelets for studies on metabolism and preservation. Tullis reports a lack of correlation between morphology and functional integrity in a study of leucocyte survival. Ameboid motility and phagocytic ability are believed to approximate functional viability most closely.[382] Granulocytes transfused into irradiated dogs with aplastic marrows migrate to sites of infection.[383]

In contrast to metabolically active leucocytes, platelets appear relatively inert and are preserved for longer periods of time than other formed elements. Normal morphology is exhibited longest in platelets originally collected in plastic bags containing acid citrate dextrose (ACD) solution.[384] Exposure to glass, or the use of ethylenediamine tetraacetate instead of citrate, causes platelet morphology to change from thin, flat disks to spiny basically spherical forms.[585] No correlation existed between the morphology of preserved platelets and their functional behavior.[384]

Platelet survival in transfused patients varies between one and three days (Tullis). The clinical effectiveness of such transfusions in thrombocytopenic patients is greater than would be expected from the slight rise in total count.[384] The life span of platelets determined by C^{14}-labeled formate administration is three to four days.[386] Stefanini found survivals of four to five days when platelet-rich polycythemic blood was transfused into patients with secondary thrombocytopenic purpura.[387] No reactions occurred in 21 cases of transfusions with freshly prepared platelets.[388]

Plasma Fractions and Volume Expanders.—The administration of specific blood components for the treatment of specific blood deficiencies may be more feasible in the future with the further development of biomechanical equipment.[389]

The plasma expanders, dextrans, polygelatins, and polyvinylpyrrolidone (P.V.P.), are lifesaving in animal experiments and in clinical use. With any of the plasma substitutes, however, false security must be avoided and the need for whole blood kept in mind.†

There is considerable variation in dextran products available in Sweden, Britain, Australia, and the United States, and the molecular weights range from 20,000 to 250,000. Smaller particles are rapidly eliminated by the kidneys, while larger particles are readily phagocytosed but remain in the blood stream longer. ‡ There is no agreement on the ideal molecular weight. It is probably higher than the 36,000 average molecular weight of products currently in use.[399] Others have recommended higher (130,000 to 250,000) molecular weight ranges.[396] Relatively homogenous dextran fractions for physiologic evaluation have been prepared.[400]

Reports on the antigenicity of dextran fail to emphasize that there is a considerable difference between the various products in use. Both native and clinical

* References 380 and 381.

† References 390-393.

‡ References 394-398.

dextrans are antigenic in man.[401] No reports of severe reactions have appeared, but a high percentage of patients show mild reactions.[402] These mild reactions are less marked with the newer products.[390]

Studies on C^{14}-labeled dextran indicate that in a nine-day period about 11% is metabolized.[399] Urinary excretion accounts for the majority of dextran leaving the blood in the first hour after injection. Only a small amount is retained in the intravascular spaces, and the concentration in lymph from mesentery and muscle is about 1/10 that of blood.[403] An excellent histochemical study of the fate of dextran in mice demonstrated it in liver cells, renal tubules, and widely scattered phagocytes of the reticuloendothelial system.[397]

Repeated dextran infusions result in marked diuresis. A group of 10 nephrotic children receiving dextran lost weight and showed clinical improvement.[404] Dogs receiving dextran show no significant changes in plasma proteins, glomerular filtration rate, or general health.[405] Dextran infusions produce a uniformly fatal reaction in adrenalectomized rats. Cortisone prevents the cyanosis and death but not the edema.[285] Preliminary studies on hydrodextran have found it to be stable over a six-month period of storage.[406]

Polyvinylpyrrolidone was used as a plasma expander in 52 cases of impending or real shock without ill effect and with benefit in 44 cases.[407] Due to a species sensitivity, dogs may show severe reactions to P.V.P.; this is marked with the small-molecular-weight fractions.[408] Modified fluid-gelatin has been found to be more effective than dextran or oxypolygelatin in the treatment of dogs with experimental hypotension of one hour's duration.[409] Globin is not satisfactory as a plasma expander.[410]

Transfusions.—The ill effects complicating blood transfusions can be classified as follows: (1) pyrogenic, (2) contaminated blood, (3) citrate intoxication, (4) disease transmission, (5) allergic, (6) circulatory overload, and (7) hemolytic.[411] Immunologic transfusion reactions are discussed on page 657. The use of antihistaminics decreases the frequency and severity of allergic and pyrogenic transfusion reactions. Its routine prophylactic use is suggested.§ Two types of reactions due to Gram-negative bacteria contamination have been reported. One of these is characterized by a shock-like state and bacteremia. The other is a fatal pyrogenic reaction produced by cold-growing bacteria.[414] Routine bacterial staining immediately before the administration of every blood is advised.[415]

Hemoglobin decreases 13% and the average hematocrit level falls 11.7% after blood donations.[416]

Sodium citrate does not exert an in vivo anticoagulation effect after massive blood transfusions.[417] However, critically ill patients, particularly those with liver damage or impaired hepatic circulation, do not tolerate large amounts of citrate. This may explain some instances of profound hypotension during apparently adequate blood replacement.[418]

The importance of proper precaution in screening donors has been reemphasized. About 2% of Red Cross blood donors are disqualified because of a history of jaundice (1.71%) or because of exposure to jaundice within six months (0.23%).[419] In spite of careful screening, the homologous serum jaundice virus

§ References 412 and 413.

is found in donors with no history of exposure or recent injections.[420] Irradiation of plasma leads to some improvement but does not prevent the development of homologous viral hepatitis in patients receiving plasma transfusions.[421]

Intra-arterial blood transfusion has advantages over intravenous infusion in critically exsanguinated patients. This may be due to elevation in general systemic and coronary artery pressures, resulting in an increased coronary flow.‖ Results of some animal experiments are in contradiction to this theory, however.[424] Rapid transfusion in animals does not cause prolongation of bleeding from an open vessel, nor does bleeding resume from previously formed clots.[425]

High rates of administration (300 ml. per minute) have been recommended for intra-arterial transfusions in man. However, there is danger of elevated potassium levels in stored blood reaching the heart in toxic concentrations.[426]

Gangrene has followed intra-arterial transfusion in patients with inadequate collateral circulation. Methods of avoiding this are described.[427] Anemic or hypoproteinemic dogs tolerate intra-arterial transfusions as well as or better than normal dogs.[428] A method of intra-aorta blood transfusion is described and "has proven simple and free from complications in 20 cases." [429]

A blood-drawing technique involving puncture of the torcular Herophili through the posterior fontanel of infants has been described. In emergencies, transfusions can be administered into the straight sinus.[430]

Blood Volume.—The Evans blue dye (T-1824) method for studying the circulating blood volume has been evaluated.[431] A modification of this method based on spectrophotometric absorption at 440, 620, and 710 mμ is effective even in the presence of hemolysis and/or lipemia.[432] The relative merits of the multiple sample technique and the single sample method are controversial.¶ Comparison of the Evans blue method with other techniques indicates that (1) the radioactive iodinated human albumin technique is easier [435] and (2) the sulfobromophthalein method gives values 5.5% lower.[436]

The finger hematocrit level approximated the total body hematocrit level more closely than did that of venous blood.[437] The ratio of total body hematocrit level to the venous hematocrit level was found to be 0.91,[438] 0.91,[439] and an average of 0.924.[433] This ratio varied from 1.1 in dogs with dilated spleens to 0.9 in dogs with empty spleens [440]; a value of 0.87 was obtained in splenectomized dogs. This could be made to fall below 0.80 by the infusion of large amounts of dextran solution, although the ratio remained constant in dogs receiving packed red cells.[441]

Radioactive chromium (Cr^{51}), with a half-life of 26.5 days, is also used for the determination of plasma volume. The in vitro tagging of proteins is unnecessary, since about 98% of chromic chloride administered parenterally is rapidly bound by the plasma proteins.[2] The sodium chromate form of Cr^{51} remains in the plasma longer than other forms of the substance.[442] The simultaneous determination of red cell mass and plasma volume may be made by the combined use of radioactive sodium chromate and chromic chloride. The results compare favorably to the use of these materials separately.[439]

Blood volume in pregnancy has been studied by use of P^{32}-labeled erythrocytes. In addition to the well-known hydremia of pregnancy, there is a decrease in the

‖ References 422 and 423.
¶ References 433 and 434.

total red cell mass in the first and second trimesters.[299] Creation of an arteriovenous fistula between the aorta and the inferior vena cava has been found to increase plasma volume of dogs by about 30%. In the two-to-six-week period following surgery, however, red cell volume does not change significantly.[443]

Macrocytic Anemias

Recent highlights are (1) a masterful review by Castle on "Development of Knowledge Concerning the Gastric Intrinsic Factor and Its Relation to Pernicious Anemia" appearing in the *New England Journal of Medicine* [444] (reference to the original article is strongly recommended), (2) the oral treatment of pernicious anemia with small doses of Vitamin B_{12} combined with mucosal materials derived from hog stomach, and (3) the development of tests which will give evidence of pernicious anemia existing even in remission.

"Pernicious anemia is still a conditioned deficiency disease." [445] Castle described the whole matter very succintly:

> The disease would not develop if the patient could effect daily the transfer of a millionth of a gram of vitamin B_{12} the distance of a small portion of a millimeter across the intestinal mucosa and into the blood stream. This he cannot do, principally as a result of failure of the stomach to secrete into its lumen some essential but still unknown substance. Yet the patient may each day absorb without much difficulty the products of the digestion of many grams of carbohydrate, fat, and protein from foods that in addition may contain consequential amounts of vitamin B_{12} in terms of his trivial need.[444]

The biochemist has effected preparations from hog stomach (containing the intrinsic factor) which, combined with relatively small amounts of vitamin B_{12}, make a satisfactory oral preparation for bringing about full remission and maintenance of patients with pernicious anemia.#

A word of caution is injected here. It should be remembered that the physician's primary responsibility to the patient with pernicious anemia is (1) the arresting or prevention of the C.N.S. combined system disease and (2) the discovery of the rare, resectable gastric carcinoma. The anemia is reversible, but these complications may not be. Monthly parenteral therapy in most patients with pernicious anemia has created a certain discipline which allows the physician to make periodic checks for these complications. Oral therapy lessens this discipline and may allow the patient a false sense of security, which may result in less frequent examinations.

This "progress" has resulted in a heyday for many pharmaceutical houses, who have taken the combined stomach concentrate and vitamin B_{12} and have added iron salts, ascorbic acid, folic acid, et cetera, creating "a comprehensive formula for all the treatable anemias." The intensive advertising campaigns through which the shotgun antianemia mixtures are being projected will undoubtedly spread the evil of shotgun therapy even further. "There is no justification for indiscriminate medication and such a practice is obviously dangerous as well as unsatisfactory." [450] "Blunderbuss preparations are dangerous because they prevent accurate diagnosis." [451] Pernicious anemia carries with it a sentence of life-time therapy. Shotgun therapy clouds the picture, and, if it is continued, one is unable to ascertain which elements in the shotgun have benefited the patient.

References 446-449.

The diagnosis of pernicious anemia in the face of adequate therapy has been and continues to be quite a problem. However, the development of new approaches, still in the investigative stage, seems encouraging. The absolute diagnosis of pernicious anemia rests on demonstrating the absence of the intrinsic factor. 1. Castle's classic bioassay is extremely complicated. 2. Radioactive cobalt incorporated in vitamin B_{12} when given orally to the pernicious anemia patient can be recovered in large part in the feces.* 3. Schilling has refined this by giving a small dose of radioactive vitamin B_{12} orally followed in two hours with 1,000 γ of nonradioactive vitamin B_{12} by subcutaneous injection. Beginning about four to six hours after the oral dose, radioactivity appears in the urine for at least 24 hours. Patients with pernicious anemia excrete no radioactive substance in the urine.† 4. If the urorennin activity reflects the pepsin and rennin activity of the gastric secretions, Olmstead and Hirschboeck assume that low urorennin levels should occur in those diseases associated with atrophy of the gastric mucosa. In standardizing the test and applying it to 50 patients with pernicious anemia in remission, they concluded that if a patient excreted more than 0.5 rennin units per 10 cc. of fasting morning urine it was extremely unlikely that the patient had pernicious anemia. If, however, the excretion was less than this amount, the patient may or may not have pernicious anemia, and further study is indicated.[456] 5. Rubin and Massey note a characteristic appearance of the exfoliated cellular material from the stomach of patients with pernicious anemia, persisting despite prolonged therapy. "Chymotrypsin lavage" and the "antrol abrasive balloon" provide excellent cytologic material. Two types of atypical columnar cells have been demonstrated. Type I cells are enlarged and contain nuclei approximately twice normal size, varying from a round, bland to an irregular, hyperchromatic, almost anaplastic appearance. Type II columnar cells are slender and elongated, containing either small pyknotic or large vesicular nuclei, centrally located in the cell. Various gradations exist between these two extremes. Type I cells seem specific for pernicious anemia and were demonstrable in 20 of 21 patients who had been adequately treated from 1.3 to 23 years (average, 7.5 years). Untreated patients with pernicious anemia also were examined for comparison.[457]

There is no complete agreement on the relationship of the atrophic gastric mucosa and pernicious anemia.[458] On one hand, Dailey and co-workers assert that the association of pernicious anemia and atrophic gastritis is not universal. Thirteen of 25 treated patients with pernicious anemia had no gastroscopic evidence of atrophic gastritis. Conversely, of 95 patients with atrophic gastritis, 12 had pernicious anemia. In 15 patients with atrophic gastritis, 7 had definite anemia, microcytic in 4, normocytic in 1, and macrocytic in 2.[459] Gastric atrophy is not appreciably changed by therapy.‡

Biochemistry and Pharmacology of the Antimegaloblastic Substances.—An outstanding summary of the biochemistry of folic acid and vitamin B_{12} in the physiology of vertebrates has been made by Jukes.[461] A similar short summary on vitamin B_{12} has also been published by Rubbo.[462] Another excellent review, directed more particularly to recent advances in fundamental research in pernicious

* References 452 and 453.

† References 454 and 455.

‡ References 457 and 460.

anemia, appeared in a Lancet editorial.[445] Reference to these original articles is suggested. Several chemical types of vitamin B_{12} are now recognized: vitamin B_{12a}, containing a cyano group (cyanocobalamin); vitamin B_{12b}, containing a hydroxyl group (hydroxycobalamin); vitamin B_{12c}, in which the cyano group of vitamin B_{12a} is replaced by nitrite, and vitamin B_{12d}, the product of the removal of the nitrite group of vitamin B_{12c}.[462] Vitamin B_{12b} is less potent as an antianemic agent than vitamin B_{12a}.[463] Vitamins B_{12a} through B_{12e} have been reported effective in the treatment of pernicious anemia. Crystalline vitamin B_{12f}, isolated from rat feces, is not effective.[464] Lactobacillus leichmannii, Escherichia coli mutants, and Euglena gracilis micro-organisms have been used in the microbiological assay of vitamin B_{12}. These organisms respond to other substances in addition to true

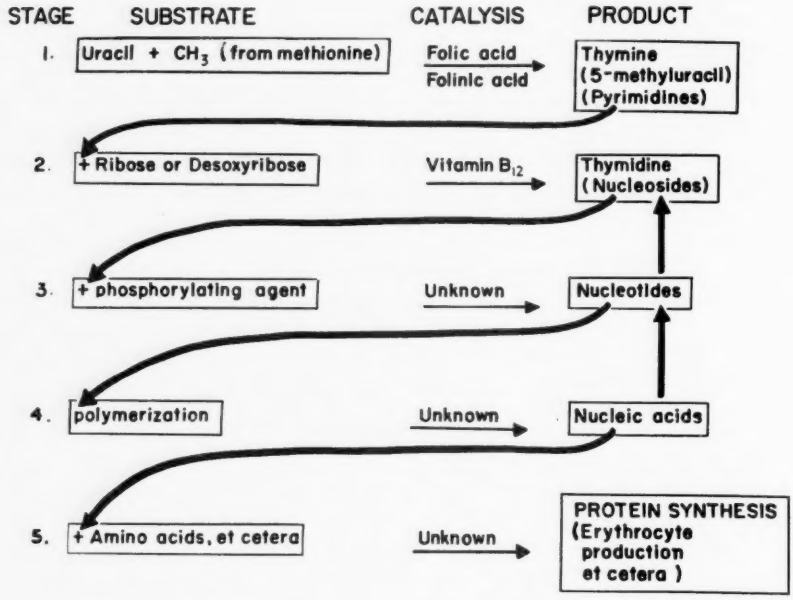

Fig. 1.—Diagram of the enzymic mechanisms in erythrocyte production. Modified from Rubbo,[462] *The Medical Journal of Australia.*

vitamin B_{12}; hence other test organisms have been sought that would respond to pure vitamin B_{12} only. The chrysomonad Poteriochromonas stipitata has been found effective in preliminary studies.§

The relation of vitamin B_{12} to growth and reproduction continues to be investigated.‖

A simplified diagram of the mechanisms of the pathologicochemical reactions of megaloblastic anemias has been outlined by Rubbo[462] (Fig. 1).

Wallerstein and co-workers have continued their fundamental studies on the role of vitamin B_{12} in pernicious anemia, and their most recent observations confirm

§ References 465 and 466.

‖ References 467-471.

the previously proposed theory that the essential physiologic function of intrinsic factor is merely to enhance the assimilation of vitamin B_{12}. They indicate the possibility that the primary effect of the intrinsic factor is upon the intestinal wall rather than upon the vitamin B_{12}.[472]

Related to the previously mentioned work on the increased fecal excretion of Co^{60}-labeled vitamin B_{12} in pernicious anemia, similar observations have been noted in a patient who had a total gastrectomy.[473] The old question of a relative pernicious anemia was again argued. Movitt and Lubeck assert that the difference between a normal person and a patient with pernicious anemia with regard to the intrinsic factor may be quantitative rather than qualitative in some instances.[474]

May and associates have confirmed their original observations that the net effect of scurvy in monkeys is to cause increased requirements for folic acid compounds which cannot be met by the supply of these compounds obtainable from the milk diet and the feces.[475] Further work along these lines indicates that the normal relationship of ascorbic acid to its oxidation product, dehydroascorbic acid, is altered and that this alteration is corrected by specific therapy in pernicious anemia.[476] Other basic studies on the interrelation of these antimegaloblastic substances have been made in chicks [477] and in premature infants.[478]

Arrowsmith and co-workers report a case of aregenerative anemia in an 18-month-old child; it was characterized by severe diminution of nucleated red cells in the marrow. Although this anemia was refractory to vitamin B_{12} and folic acid, cortisone inaugurated erythropoiesis, with an initial reticulocytosis. The red cells appeared to be macrocytic, and the bone marrow at this time was megaloblastic. Administration of vitamin B_{12} and folic acid produced a second reticulocytosis, with subsequent rise in hemoglobin. Cortisone was discontinued, and the patient reverted to pretreatment status despite continued administration of vitamin B_{12} and folic acid. Combined cortisone, vitamin B_{12}, and folic acid therapy again produced a remission.[479] Refinement and extension of the techniques for measuring the antimegaloblastic substances in the serum and urine have contributed greatly to the basic understanding of the mechanisms involved in both health and disease.¶ Biochemical and cytological studies of bone marrow cells, both in vitro and in vivo, have also resulted in significant contributions.#

Miscellaneous Observations in Pernicious Anemia.—Prothrombin concentration (by the methods of Owren and of Ware and Seeger) was diminished in approximately 50% of 40 patients with pernicious anemia in remission. These patients had been on vitamin B_{12} therapy for more than two years. There was no correlation between these findings and standard liver-function tests.[496] The cerebral blood flow was found to be increased in untreated patients with pernicious anemia and was proportional to the decrease in red cell mass. Even in the two patients with striking neurologic changes, there was normal cerebral oxygen consumption.[497] James and Abbott measured the life span of erythrocytes that were formed during reticulocytosis in therapeutically induced remissions in megaloblastic anemias. The observed average life span of these cells was about 114 days; red blood cells produced under the stimulus of rapid erythropoiesis had a normal life span.[498] The red blood cell survival time during exacerbation of the anemia is shortened, and there

¶ References 480-491.

References 492-495.

is evidence that most of the hemoglobin pigment metabolized is not derived from circulating erythrocytes. Coleman and Finch have studied erythropoiesis in pernicious anemia, utilizing determinations of serum iron turnover, red cell utilization of radioiron, bone marrow differential counts, serum bilirubin, reticulocyte counts, and stool urobilinogen. They conclude that, while red cell delivery from the marrow to the peripheral blood is subnormal, hemoglobin synthesis and degradation within the marrow occurs at a rapid rate. This intra-marrow hemolysis ceases with vitamin B_{12} therapy; synthesized cells are then delivered in large numbers to the peripheral blood. Once a source of iron derived from intramedullary erythrocyte destruction is cut off, hemopoiesis is limited by the rate at which tissue iron can be mobilized.[499]

Treatment of Pernicious Anemia.—Several excellent reviews have appeared.* Meacham and Heinle found that a daily dose of vitamin B_{12} averaging 1 γ per day, given intramuscularly at intervals of three to four weeks, appears to be sufficient to maintain normal red cell levels and to prevent the development or progression of neurological and lingual lesions. Slight macrocytosis persists in many of the patients, however, and it was not altered by intramuscular administration of purified liver extract or by the addition of daily oral doses of folic acid. They suggest that neither vitamin B_{12}, purified liver extract, nor folic acid, given singly or in combination, completely corrects the erythrocyte abnormality in pernicious anemia and that some other substance(s) may be necessary in addition.[502] Amounts of vitamin B_{12} above a threshold value of 25 to 50 γ by injection are rapidly and quantitatively excreted in the urine. Therefore massive single injections of vitamin B_{12} cannot be substituted for more frequent regular injections of smaller doses.[503]

Crystalline vitamin B_{12} inhalation therapy is effective in pernicious anemia. It is administered either as vitamin B_{12} in isotonic sodium chloride solution or as vitamin B_{12} lactose powder.† The varying results that have been obtained by Watson and co-workers in the use of citrovorum factor in megaloblastic anemias again emphasize our lack of understanding of the interrelationships of citrovorum factor to vitamin B_{12}.[507]

Nutritional Macrocytic Anemias.—Das Gupta and co-workers point out that nutritional macrocytic anemia cases in different parts of the world may vary in their degree of deficiency of vitamin B_{12} and folic acid, depending on the dietary habits and the gastrointestinal conditions. The response to vitamin B_{12} and/or to folic acid depends on both absolute and relative deficiency of the two factors, which may explain the difference in response obtained by workers in different places. In their series, in India, deficiency of folic acid was the major factor.[508] In an East African group of megaloblastic anemias, Foy and co-workers induced remissions with penicillin in some cases. The antibiotic was effective only in proper dosage; too little had no effect and too much was equally unsuccessful. One of the proposed hypotheses is that the optimum doses destroy some intestinal organisms that compete for the antianemic factor, while excessive doses destroy those micro-organisms that can synthesize it. Foy divides his megaloblastic anemias into three classifications: Type 1 responds to penicillin and all known hematinics; Type 2 does not

* References 500-502.

† References 504-506.

respond to penicillin or oral vitamin B_{12} but does respond to intramuscular vitamin B_{12}; Type 3 responds only to folic acid.‡ Type 2 patients have atrophic gastritis and complete achlorhydria.

Megaloblastic Anemia and Infections.—This subject has been reviewed in *Nutrition Reviews.* Experimental work apparently indicates that scurvy, respiratory infections, or turpentine abscesses in the experimental animal creates an increased demand for folic acid and that if this is not present in the diet megaloblastic anemia can develop, at least in the monkey.[510]

Leiner's disease (erythrodermia desquamativa) occurs in children and is associated with the indicated skin lesions, steatorrhea, macrocytic anemia, and progressive weight loss. The macrocytic anemia along with the general clinical state improves markedly with vitamin B_{12} therapy.[511]

Macrocytic Anemia of Pregnancy.—The last word on proper therapy for this state is still to be heard. It has been felt that folic acid is specific[311]; however, occasional exceptions have occurred.[312] In Cohen's report of five cases of postpartum megaloblastic anemia in Africans, the response to therapy was variable and unpredictable. Case 1 responded to vitamin B_{12}; Case 2 responded to folic acid and not to vitamin B_{12}; Case 3 responded to neither penicillin nor folic acid but to vitamin B_{12}; Case 4 showed a partial response to vitamin B_{12} and a complete response to folic acid; Case 5 showed no response to penicillin but responded rapidly to folic acid.

Megaloblastic Anemia Associated with Diphyllobothrium Latum Infestation.—Interesting observations from the Finnish investigators continue. Von Bonsdorff concludes that the anemia is due to the competition for vitamin B_{12} between the parasite and the host, thus creating the deficiency. He believes that if the worm is situated in the initial part of the small intestine a concurrent decreased intrinsic factor production may contribute to the deficiency.[512] Björkenheim in 1951 showed that neurologic changes of subacute combined degeneration of the spinal cord and peripheral nerve degeneration were present in 75 of 95 patients with megaloblastic tapeworm anemia. The worm cure alone or in combination with liver or vitamin B_{12} therapy resulted in extensive or complete neurologic remissions. The neurologic course was unfavorable in one case only, and this patient was treated with folic acid.[513]

The Anemia of Scurvy.—This anemia is normochromic and normocytic in the majority of cases. Only rarely, in the severest cases, is the anemia macrocytic, with a corresponding megaloblastic bone marrow. Bronte-Stewart found anemia in 26 of 32 adult Bantu Negroes with scurvy.§ Treatment with iron, folic acid, and vitamin B_{12} had no effect on the anemia or the bone marrow. Ascorbic acid alone corrected the anemia, even in the rare macrocytic type. This is in line with May's experimental observations in monkeys.[475]

Iron Deficiency Anemias and Disturbances in Iron Metabolism

Iron Metabolism.—Iron-deficient dogs absorb more iron than normal dogs, but the plasma iron level does not affect iron absorption from the intestine. Rather, the

‡ References 445, 501, and 509.

§ References 514 and 515.

mucosal block is the controlling factor (radioiron absorption is depressed in iron-deficient dogs if they are given ordinary iron previously). Deficiency of body copper decreases iron absorption in rats. Diets with corn serving as the protein source lead to increased iron absorption (the phosphate level seems to be the critical factor).[517] The relationship between tissue ferritin, hemoglobin, and hemosiderin iron has been studied by a quantitative fractionation method. After a certain level of total body iron is reached, iron is no longer stored as ferritin but as hemosiderin. Hemosiderin is thought to be aggregates of ferritin molecules.[518] The value of radioiron in hematologic studies is again emphasized.[519]

As hemosiderin is a compound composed of iron hydroxide in various combinations, it is subject to the same physicochemical alterations as is iron hydroxide. Freshly precipitated iron hydroxide is an amorphous gel. As the gel ages, it assumes a crystalline mineral structure, producing characteristic interference lines on roentgenograms. Hemosiderin precipitated in vivo is also subject to this structural change. This crystallization process is thought to make the iron of hemosiderin essentially unavailable to the body for synthesis, since it cannot revert to the chemically reactive amorphous colloidal state.[520]

Copper deficiency in pigs results in hypochromic, usually microcytic, anemia and leucopenia. Copper-deficient pigs do not absorb iron normally nor can they mobilize it from the tissues. The presence of copper in rats increases the retention of radioiron. This does not depend on the simultaneous administration of copper with the iron; therefore, copper levels in the tissues rather than the level of copper in the diet is the critical factor.[521]

From 20 to 80% of the marrow normoblasts of nonanemic subjects (infants and children) contain iron granules, as demonstrated with the Prussian blue reaction. Similar figures are obtained in hemolytic anemias and anemias associated with erythroid hypoplasia (renal disease, infectious aplastic anemia). Iron granules are consistently decreased in hypochromic microcytic anemia due to iron deficiency but are elevated in thalassemia. This indicates a fundamental difference between these superficially similar anemic states.[522]

The iron-binding capacity of serum is the difference between serum iron already combined with siderophilin and the capacity of serum to take up more iron. A low serum iron combined with a high total iron-binding capacity is practically diagnostic of iron-deficiency anemia. In the anemia of chronic infection, serum iron and total serum iron-binding capacity are low.[523] Subnormal rates of plasma and red cell iron turnover are found in patients with erythroid hypoplasia. Similar findings may be expected in any disease causing an interruption in erythropoisis at stages prior to those capable of incorporating iron. In contrast, excessive plasma iron turnover characterizes anemias in which erythropoiesis is interrupted at a stage capable of incorporating iron. In these cases the turnover in plasma may be via production and destruction of cells or cellular debris.[524] Changes in plasma iron concentration correlate well with plasma iron clearance as the total body iron is altered. Neither of these values is a reliable index of the hemopoietic rate, however. The plasma iron turnover reflects more closely the true hemopoietic rate, but the quantity of iron exchanged is invariably in excess of that required for hemoglobin synthesis.[525] Duck erythrocytes suspended in duck plasma incorporate radioiron into their hemo-

globin. Human erythrocytes take up only one-fifth as much in an equal time.[526] X-radiation combined with phenylhydrazine produces anemia and increased serum iron in rats. Splenectomized rats fail to develop anemia.[527]

Minimal normal values in pregnancy are: hemoglobin, 11.5 gm. per 100 cc., red blood cells, 3,700,000, and hematocrit level, 35%. In the absence of other specific anemias, a hemoglobin decrease below 11.5 gm. per 100 cc. is associated with a decrease in serum iron and an increase in the erythrocyte protoporphyrin, indicative of iron deficiency. These latter procedures are suggested as adjuncts to accuracy in diagnosing iron-deficiency anemia of pregnancy.[300]

Human subjects previously depleted of iron by venesection have more rapid hematocrit depression than subjects with normal iron stores.[528] The normal diurnal variation of the serum iron level is diminished in aplastic anemia, untreated pernicious anemia, and untreated iron deficiency anemia. Treatment restores a normal diurnal variation. Low serum iron levels and diminished diurnal variation are seen in conditions of increased erythropoiesis (polycythemia vera, congenital hemolytic anemia, nocturnal hemoglobinuria, pernicious anemia at the height of the reticulocyte response, and suboptimally treated iron-deficiency anemia). Increased diurnal variation of serum iron levels in erythropoietic disorders may be related to the increased plasma iron turnover. Corticotropin and cortisone demonstrate no effect on the diurnal serum iron levels in this case.[529]

The distribution of ingested iron was followed in mice after administration of radioactive iron. Liver, spleen, and kidney iron decreased daily following initial increases, while lung iron stores increased. The bone marrow is apparently the main destination of the iron stored in the liver and other organs. The increase in lung iron is probably related to wandering macrophage activity.[530]

Iron Therapy.—The importance of supplemental medicinal iron administered early in gestation has been emphasized in an extensive review of iron deficiency in pregnancy.[301] Actual postpartum anemia (beyond the physiologic hydremia of pregnancy) is commoner than is usually recognized.[302]

It is claimed that food alone cannot generally supply the necessary increment of supplemental elemental iron needed in hypochromic iron-deficiency anemia of nutritional origin but that it must be augmented by medicinal iron.[531] The customary fall of hemoglobin values after the 20th week of life does not occur when supplemental ferrous sulfate or ferric ammonium citrate is added to the diet.¶

Improper intravenous iron therapy utilizing saccharated ferric oxide sometimes results in toxic reactions, including flushing of the face, nausea, headache, and abdominal cramps. A sudden transitory leucopenia has also been noted after administration of a colloidal solution of iron oxyhydrate. Other colloids produce leucopenia by causing dilatation of the pulmonary vascular channels, with resultant leucocyte storage.[534] Some of the toxic effects may be the result of anaphylactic reactions.[535] Indications for intravenous iron therapy are (1) true iron-deficiency anemia unresponsive to oral iron, (2) intolerance to oral iron, (3) allergy to oral iron, (4) iron-deficiency anemia discovered late in pregnancy, and (5) severe hemorrhage in patients in whom transfusions are prohibited for religious reasons.[534]

Total gastrectomy in rats produces severe hypochromic microcytic anemia with low serum iron and normal iron-binding capacity. This responds to intravenously

¶ References 532 and 533.

administered iron.[536] In a report from Cairo, intravenous iron therapy resulted in a rise in hemoglobin in anemias due to Ancylostoma infestation and hemorrhagic states.[537] Warning should be made again about the indiscriminate use of intravenous iron.

Cobalt.—Cobalt is intimately associated with certain aspects of erythropoiesis. A lack of dietary cobalt may cause anemia in sheep and cattle. Cobalt feeding will produce a true polycythemia in a number of experimental animals and birds. The mechanism is not clear. Several recent publications have claimed more effective erythrocyte and hemoglobin production in iron-deficiency anemia treated with cobalt and iron preparations than in that treated with iron alone. Increases in platelets and leucocytes may be associated.[537a] Benefit is also claimed for cobalt chloride in hypoplastic anemias ¶¶ and in anemias of chronic renal disease [537c] and infection. The erythropoietic response to cobalt lasts only for the duration of the treatment. More extensive clinical trials are necessary before any concrete evaluation can be made. Cobalt therapy is not innocuous. It may be associated with anorexia, nausea and vomiting, skin reactions, parasthesias, thyroid hyperplasia, coronary type chest pain, and sudden death. Cautiousness must be emphasized.[537d]

Hemochromatosis and Hemosiderosis.—In hemochromatosis total body iron is increased and this is accompanied by liver cirrhosis. In hemosiderosis particular tissues contain excess iron but may be functionally and morphologically normal.# Hemochromatosis has been regarded as of two types, endogenous (idiopathic—the increased iron is absorbed through the gastrointestinal tract) and exogenous (the transfusion type). Frequently in the so-called exogenous hemochromatosis the quantity of iron present in the body exceeds that administered by transfusions. It is postulated that the anemia may cause an increased iron absorption from the gastrointestinal tract in this type also and that the transfusions only hasten the entire process, rather than being the primary cause. Thus, prolonged iron therapy to an unresponsive anemic patient may be distinctly harmful.[538] A case of chronic hemolytic anemia was complicated by hemochromatosis due to prolonged oral iron therapy.[540] A similar situation developed in a case of Cooley's anemia.[517] Iron absorption is probably increased in both primary and secondary hemochromatosis.[539] Anemic dogs absorb iron to a much greater extent than do normal dogs. It has been postulated that the hypothetical ferritin mechanism ("mucosal block") is disrupted owing to the hypoxia of anemia altering the redox level of mucosal cells. This allows the cells to absorb excess iron.[541]

Patients with hemochromatosis utilize a portion of administered radioiron for hemoglobin formation; the remainder is deposited largely in the liver. In malnutritional cytosiderosis the absorption of iron from the intestine was low in four of five cases, which is confusing and not satisfactorily explained.[542] Hemochromatosis has been observed to follow an attack of severe homologous serum jaundice.[543]

The clinical features of hemochromatosis have been reviewed.[544] Conjunctival microaneurisms and retinopathy have been observed in hemochromatotic diabetes.[461] Also, there may be a high degree of insulin resistance.[547] Heart involvement in hemochromatosis may produce congestive failure without evidence of the commoner types of heart disease.* Idiopathic hemochromatosis improves strikingly following

¶¶ References 203 and 537*b*.

References 538 and 539.

* References 545 and 546.

repeated phlebotomy.[548] The procedure must be instituted early.[549] Dimercaprol (BAL) treatment was followed by clinical improvement in one case.[550]

Pulmonary hemosiderosis occurs in children and young people and is characterized by periodic attacks of dyspnea, cyanosis, and hemoptysis. Massive hemosiderosis in the lungs exclusively has been found on autopsy.[551] Hemorrhages may occur owing to an allergic reaction (in one case there was a positive direct Coombs test and a raised hemolytic activity of the serum) [552] or the elastic tissue of pulmonary vessels may be defective.[553] Aspiration lung puncture yields macrophages packed with hemosiderin granules. This procedure is suggested for establishing the diagnosis in questionable cases.[554] Sideroblasts are discussed under iron metabolism.[522]

Methemoglobinemia.—Primary congenital methemoglobinemia is due to a congenital metabolic dysfunction in which the body cells lack an enzyme system which normally keeps hemoglobin in its reduced form.†

Aromatic nitro and amino compounds cause methemoglobinemia. Compounds of these types have been treated with radioiodine (I^{131}) and have been found to be firmly bound to red cell hemoglobin. The resultant methemoglobinemia soon disappears, leaving the radioactive material within the red cell.‡ Both methemoglobin and sulfhemoglobin were found in 100 analyses of human blood samples. The absorption bands of these two compounds are so similar that both pigments are measured simultaneously unless special care is taken.[559]

Care should be taken not to label cyanotic patients, often children, as congenital heart disease cases when methemoglobinemia may be the cause.[560] Secondary methemoglobinemia responds to intravenous or oral methylene blue. Large doses produce toxic symptoms. Methylene blue opens a new reduction pathway in the erythrocyte in addition to accelerating the usual mechanism of conversion.[556] Primary methemoglobinemia responds well to daily oral doses of ascorbic acid. It acts by direct reduction of blood methemoglobin.[556]

Porphyria.—Experimental Studies: Porphyrin synthesis involves the citric acid (Kreb) cycle.[561] As a follow-up of the observation that poliomyelitis patients excrete coproporphyrin III in the urine, the isolation of porphyrins from beef brain suggests a relation of the central nervous system to the coproporphyrin.[562] Male rats excrete two times as much urinary coproporphyrin in 48 hours as do females. Sex hormones appear to be responsible for this variation.[563] Functional liver impairment in man increases porphyrin excretion. In rats, severe liver damage does not increase the excretion of coproporphyrin but does increase the ratio of urinary to fecal coproporphyrin excretion.[564] Lead-treated rabbits excrete coproporphyrin III in the urine along with other multiple-carboxyl porphyrins.[565] Allylisopropylacetylcarbamide (Sedormid) also produces porphyria in rats.[566]

Classification, Clinical Studies, and Treatment: A classification of porphyrias by Schmid, Schwartz, and Watson follows:

(1) Porphyria erythropoietica (infantile, photosensitive, or "congenital" form, often accompanied by hemolytic anemia and splenomegaly)

† References 555 and 556.

‡ References 557 and 558.

(2) Porphyria hepatica

(*a*) Intermittently acute form (with abdominal, neurological or psychological symptoms)

(*b*) Cutaneous form (with photosensitivity, but without abdominal, neurological or psychological symptoms; usually occurring in adults)

(*c*) Combined form (with photosensitivity plus abdominal, neurological, or psychological symptoms)

This classification, involving abnormal porphyrin metabolism, is based on the porphyrin levels found in different body organs. In rabbits it has been possible to reproduce forms of erythropoietic (by lead and phenylhydrazine) and hepatic (by allylisopropylacetylcarbamide) porphyria, which are similar in some respects to the corresponding human forms.[567]

Most cases of either congenital or acute porphyria have Type I coproporphyrins or uroporphyrins. Type III uroporhyrins or coproporphyrins are also found in acute porphyria, along with two, three, five, six, and eight carboxyl-group porphyrins.[568] In a case of porphyria cutanea tarda, uroporphyrin III was isolated from bone and was microscopically localized to certain Haversian systems, depending on the mineral content.[569] Janoff and co-workers have reported a case of the "mixed" or combined variety.[570] Studies were made on patients with acute porphyria in three generations of one family.[571] Chronic congenital porphyria has occurred in two sisters.[572] Kench and co-workers report observations made on a female patient with congenital porphyria in pregnancy and postpartum and on her baby.[303]

Urinary coproporphyrin determination complements stippled cell counts or urine lead studies in diagnosis.[573]

Human porphyria has responded to dimercaprol,[574] and corticotropin has produced complete remissions in some cases.[570]

Hemolytic Anemias

Studies on Red Blood Cell Destruction.—Wasastjerna has reviewed the probable modes of destruction of sensitized red cells in vivo. The principal mechanisms in immunohemolytic disorders include (1) intravascular hemolysis, (2) intravascular agglutination with subsequent hemolysis in the spleen and other organs, and (3) phagocytosis of red cells coated with globulin.[575] In vitro erythrophagocytosis is demonstrated by neutrophiles and monocytes after incubation with peripheral blood from cases of autoimmune hemolytic disease and with blood from dogs after transfusion of incompatible plasma. Erythrophagocytosis by polymorphonuclear leucocytes is observed in the circulating blood of patients receiving heterologous blood group substances.[576] Erythrophagocytosis predominates over formation of L. E. cells when sera of patients with acute disseminated lupus erythematosus are incubated with leucocytes and erythrocytes from patients with certain hematologic dyscrasias, such as primary and secondary hemolytic anemia, Hodgkin's syndrome, polycythemia vera, chronic lymphatic leukemia, leucolymphosarcoma (acute lymphatic leukemia), Gaucher's disease, reticulum cell sarcoma, follicular lymphoma, sarcoidosis, and sickle cell disease.[577] A technique to test the susceptibility of erythrocytes to phagocytosis has been standardized. Red blood cells from patients with acquired hemolytic anemia, hereditary spherocytosis, malignant diseases, and certain infectious diseases are phagocytosed to a significantly greater degree than cells from normal persons.[578] Plasma cells of a patient with plasma cell leukemia were markedly phagocytic in vivo.[579]

Goldbloom and co-workers have demonstrated increased mechanical fragility of erythrocytes from the newborn.[580] Loss of metabolic lability of erythrocyte cholesterol[581] and exhaustion of enzyme substrate systems,[582] may be important factors in red cell ageing. Changes on the erythrocyte ultrastructure induced by various hemolysins vary with the type of hemolysin involved.[583]

The hemolytic action of 16 water-soluble ethers of glycerol has been compared with their paralyzing and toxic activities. Mephenesin possesses the strongest hemolytic and paralyzing activities.[584] Lactate accelerates oxygen uptake and hemolysis of dog erythrocytes in the presence of methylene blue.§ Comparative resistances of erythrocytes of various animal species to hemolysis by streptolysin O and saponin have been determined.[588] Rigdon has produced acute anemia in ducks with phenylhydrazine and demonstrates that the primary injury occurs in the nucleus of the red cell.[589]

The flavone, hesperidin, is absorbed into the blood stream from the gastrointestinal tract in sufficient quantities to protect erythrocytes from in vitro hemolysis by saponin.[590]

Rabbits with lowered serum sodium levels reveal no protective rise of urinary pH upon administration of hemoglobin, and subsequent cylindruria and azotemia results.[591]

Survival of transfused erythrocytes is followed by a variety of methods, including tagging with radioactive selenium,[592] radioiron,[593] radioactive nitrogen,|| radioactive Cr^{51},¶ and radioactive iodine,[602] and differential agglutination techniques.# The use of Cr^{51} in red cell survival studies has several distinct advantages: 1. It is not reutilized to tag the recipient's own cells[600]; 2. survival of the person's own cells can be measured; 3. cells can be labeled easily in about two hours, and 4. the method does not require involved technical procedures.[598] Survival time of erythrocytes in patients with lymphatic leukemia, myeloid metaplasia, and primary aplastic anemia have been studied by this method.[599] Red cell survival studies[606] and techniques have been reviewed.[371] Radioactive selenium determinations have established a life span of 11.7 days for duck erythrocytes.[592]

Virus Studies in Hemolytic Syndromes.—Clinical histories of three patients with anemia, from whom Newcastle disease virus was isolated, have been presented by Moolten and co-workers. The virus itself may have been the hemolytic factor in these patients, although autoantibodies could be found as a result of viral alteration of erythrocytes.[607] Survival of canine erythrocytes is shortened following treatment with influenza virus in vitro.[608] The panagglutinin to virus-modified erythrocytes is undetectable in the recipient's serum as long as such cells persist in the circulation. Erythrocytes modified by viruses in vitro and in vivo are more susceptible to phagocytosis by tissue culture macrophages than are normal red cells.*

Clinical Hemolytic Anemias.—Idiopathic Acquired Hemolytic Anemia: Therapy includes use of corticotropin[610]; corticotropin and cortisone,[611] and cortico-

§ References 585-587.
|| References 594-597.
¶ References 598-601.
# References 603-605.
* References 578 and 609.

tropin, cortisone, and splenectomy,[612] with variable results. Although the need for an individual approach is indicated, corticotropin and cortisone seem to induce at least temporary remissions in most cases. Splenectomy is indicated when small dosages of these drugs fail to maintain remission.[611]

Hunt and Lucia have found an increase in the incidence of blood Group O among patients with acquired hemolytic anemia. It is proposed that susceptibility to acquired hemolytic anemia may be related to the status of nonsecretion of Type A group-specific substance.[613]

Hemolytic anemia is a complication of cancer,[614] disseminated lupus erythematous,[615] and 45% of 196 cases of Hemophilus influenzae meningitis.[616] Several cases associated with pregnancy have been cited.†

Hereditary Spherocytosis: Erythrocytes of this disease are characterized by small diameter and spherical shape and are found to be capable of normal survival in the absence of the spleen.[617] Seven cases of hereditary spherocytosis occurred in two Negro families.‡ Three cases with aplastic crises have been described[620]; bone marrow aplasia was demonstrated in one patient. Hereditary spherocytes are sequestered in the spleen and rendered more susceptible to osmotic hemolysis.[621] Increased intracellular protein osmotic pressure in a case of hereditary spherocytosis was demonstrated, and a mechanism for in vivo hemolysis of spherocytes has been proposed.[622]

Hereditary nonspherocytic hemolytic anemia has been reported.[623] Splenectomy failed to produce significant improvement in several cases.§ Dacie and co-workers present four other groups of atypical congenital hemolytic anemia: macrocytosis, a variant of ellipocytosis, a variant of hereditary spherocytosis, and "triangular" red cells.[625]

Hemoglobinuria: Paroxysmal nocturnal hemoglobinuria (PNH), characterized by chronic hemolytic anemia, leucopenia, and thrombocytopenia with hemoglobinuria (usually induced during sleep), has been competently reviewed by Crosby.[626] Destruction of the abnormal cells associated with this disease is mediated through a plasma enzyme system consisting of two hemolytic enzymes and two inhibitors.[627] Small amounts of thrombin rapidly destroy the heat-stable inhibitor and, thus, increase hemolytic activity. Susceptibility of abnormal platelets to hemolytic enzymes is thought to be responsible for the thrombotic complications frequently accompanying this disease. Figure 2 illustrates the suggested relationship between the mechanisms of PNH and the blood coagulation system.[626]

Bishydroxycoumarin (Dicumarol) protects PNH patients from thrombotic accidents and sometimes relieves the anemia. It should not be used at the height of an aplastic crisis with thrombocytopenia. Corticotropin and cortisone are of no benefit and epinephrine is contraindicated.[628] Splenectomy is not indicated.[626]

Heitzman and co-workers describe a patient with PNH who showed marked scarring, tubular degeneration in both kidneys, and renal insufficiency as a result

† References 304-306.

‡ References 618 and 619.

§ References 624 and 625.

of massive deposition of hemosiderin in the tubular epithelium.[629] Incomplete cold antibody [630] and aplastic anemia [631] have also been reported to be associated with PNH.

March hemoglobinuria is characterized by hemoglobinuria and hemoglobinemia in certain young males after marching or running. Two variants from the typical picture have been reported. One patient developed the syndrome only after exercise in the horizontal position, indicating that exercise in the erect position with a lumbar lordosis is not an essential feature of the syndrome. This patient had an apparent remission of nine months' duration following corticotropin therapy. The other case is unusual in that significant hematuria accompanied hemoglobinuria after marching.[632]

Hemoglobinuria associated with the presence of cold agglutinins has been discussed on page 653, under Immunohematology.

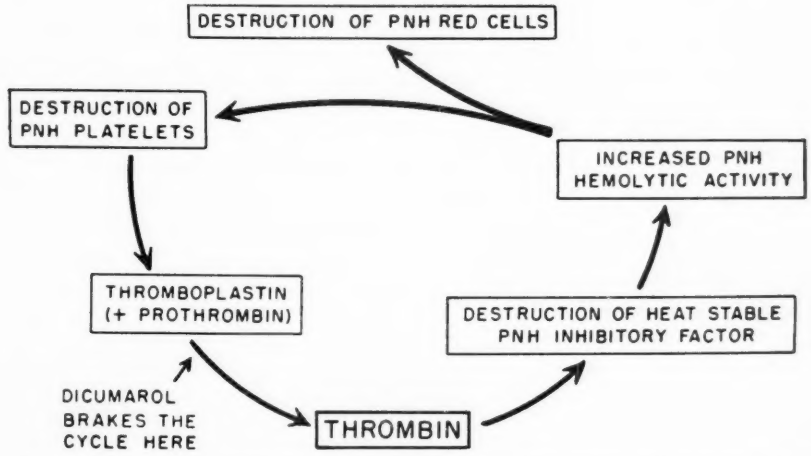
DESTRUCTION OF PNH RED CELLS
DESTRUCTION OF PNH PLATELETS
INCREASED PNH HEMOLYTIC ACTIVITY
THROMBOPLASTIN (+ PROTHROMBIN)
DESTRUCTION OF HEAT STABLE PNH INHIBITORY FACTOR
DICUMAROL BRAKES THE CYCLE HERE
THROMBIN

Fig. 2.—The "vicious cycle" that joins the blood coagulation system and paroxysmal nocturnal hemoglobinuria (PNH) hemolytic mechanism. The platelets in this disease probably possess the same PNH lesion that results in short life span of the red cells. The platelets would therefore be liable to injury by the PNH hemolytic enzymes. Thrombin increases the activity of these enzymes by destroying their powerful inhibitor. Thus, thrombin can cause increased hemolysis. The same reaction would also cause increased destruction of PNH platelets. Since injured platelets produce thromboplastin and finally thrombin, there is created a cycle that causes injury of more platelets and production of more thrombin. From Crosby,[626] *Blood*, Grune & Stratton, Inc.

Clinical Syndromes Associated with Pathological Hemoglobin Complexes: Interest in hemoglobin variants and their inheritance has reached new heights recently. Six types of hemoglobin have been recognized so far,‖ the nomenclature of which has been revised by the Hematology Study Section of the National Institutes of Health.[639] The new symbols are as follows (older designations are indicated by parentheses): normal adult hemoglobin, A (N, *a*); normal fetal hemoglobin, F (*f*); sickle cell hemoglobin, S (*b*); hemoglobin C (*c*, III, X); and hemoglobin

‖ References 633-639.

D (*d*). Subvarieties are designated by numerical subscripts. Alkali-resistant hemoglobin is identical with hemoglobin F.¶ Hemoglobin E is the most recent addition to the group.¶¶

Hemoglobins S, C, and D are considered abnormal adult hemoglobins, which may be inherited either in the homozygous or in the heterozygous state (Fig. 3).# Itano has hypothesized that hemoglobin production is the result of multiple alleles and that quantitative production is also an inherited factor.[642]

Hemoglobin F. Hemoglobin F, the predominant hemoglobin in the fetus, is associated with thalassemia, hereditary spherocytosis, aregenerative anemias, pernicious anemia, sickle cell anemia, leukemia, carcinoma with metastasis, and other miscel-

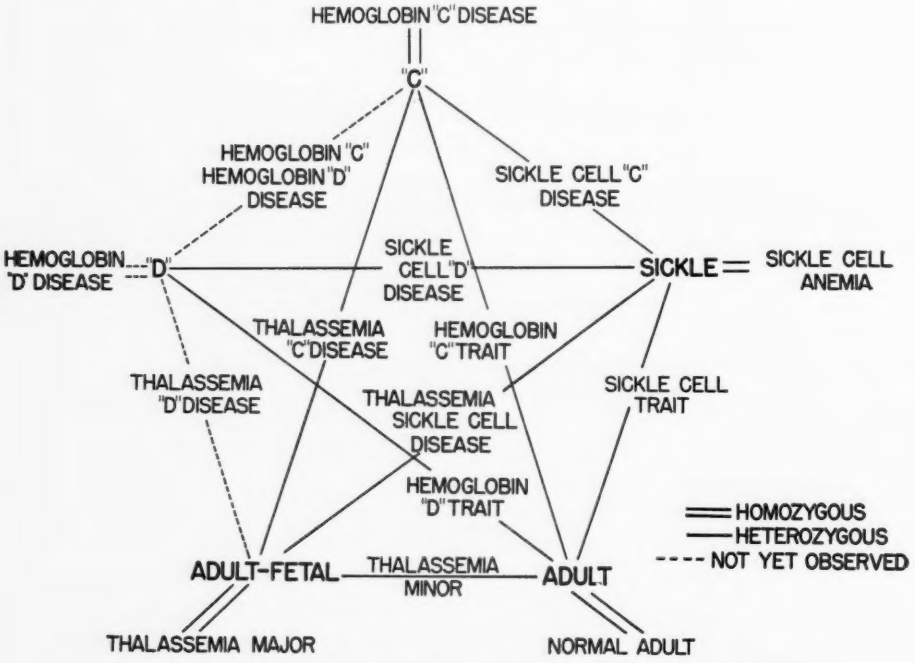

Fig. 3.—Genetic summary of the observed and postulated combinations of the human hemoglobins A, C, D, F, and S. From Newton,[635] *Ohio State University Health Center Journal.*

laneous hematologic disorders.* The presence of hemoglobin F is interpreted by some † to be an embryonic mechanism reactivated to compensate for severe anemia. Fetal hemoglobin F disappears by 7 or 8 months of age in premature infants, and hemoglobin A levels are maintained for five to seven weeks postnatally, after which a sustained rise occurs. Anemia of prematurity is due to loss of fetal hemoglobin

¶ References 322, 633, and 638.

¶¶ References 639*a*, 639*b*, 639*c*, and 639*d*.

References 322, 633-635, 640, and 641.

* References 354, 635, and 643.

† References 633 and 644.

without equivalent replacement by the adult type.[645] Fetal hemoglobin has been found rarely in children up to the age of 19 months. No fetal hemoglobin has been found in cases of kala-azar.[646] Fetal and adult hemoglobins must differ in protein moieties, since the prosthetic hemin is similar in both. "Liver" globin may be responsible for the properties of fetal hemoglobin, and "red bone marrow" globin, for those of adult hemoglobin.[647] Reported differences in oxygen equilibria of human fetal and maternal hemoglobins probably result from differences in the environment of the hemoglobin molecule rather than from intrinsic differences in the molecule itself.[648] Fetal and adult hemoglobins differ in susceptibility to alkali denaturation. Differences have also been noted in their resistances to denaturation by urea or sodium salicylate.[647] Quantitative immunologic studies disclose a greater than normal proportion of fetal hemoglobin in certain hematologic diseases.[650] Specific antihemoglobin F rabbit sera agglutinates erythrocytes of the newborn.[651]

Hemoglobin C. Hemoglobin C disease results from homozygosity of morbid genes and has been reported in several patients as a moderately severe normochromic anemia characterized by a moderate number of target cells, a mild reticulocytosis, and an absence of sickling.‡ Hemoglobin C trait results from heterozygosity of morbid and normal genes. It is asymptomatic and produces minimal abnormal hematologic findings, with the number of target cells (3 to 33%) as the only consistent hematologic variation.§ Hemoglobin C trait erythrocytes contain 30.5 to 35.3% of hemoglobin C.[653] This condition is differentiated from sickle cell trait by absence of sickling and from thalassemia minor by the absence of hypochromic microcytosis.[655] Sickle cell-hemoglobin C disease is discussed below.

Hemoglobin D. Hemoglobin D disease and hemoglobin D trait are thought to have a genetic relation similar to that of sickle cell disease and sickle cell trait. Only one family (one parent and two of the children) has been reported with hemoglobin D trait.‖ Homozygous hemoglobin D disease and hemoglobin C-hemoglobin D disease remain hypothetical, as no cases have been reported.

Hemoglobin E. In studying the genetic background of a Thai patient with what apparently was thalassemia major, it was found that only one of the parents had the thalassemia trait. Hemoglobin E was then demonstrated.[639b] Its presence was found in other Thai persons but could not be found in the blood of several hundred subjects of Caucasian, Negro, or American Indian ancestry. Hemoglobin E. was found in 12.5% of 590 persons in Thailand. The electrophoretic mobility is intermediate between hemoglobin C and hemoglobin S.[639c] Preliminary study indicates that it may exist as the trait, as "pure" hemoglobin E disease, and as thalassemia-hemoglobin E disease. Persons with hemoglobin E trait were asymptomatic. In hemoglobin E disease splenomegaly was found in three of five patients. All complained of tiredness and arthralgias, and two, of icterus. There were 25 to 60% target cells, normal erythrocyte levels, and no increase in reticulocytes. Hemoglobin analysis showed 94 to 98% hemoglobin E and 2 to 6% hemoglobin F. Thalassemia-hemoglobin E disease was manifested clinically as a moderate hemolytic anemia very similar to though somewhat milder than thalassemia major. In several patients,

‡ References 641 and 652-654.

§ References 635 and 655.

‖ References 633 and 644.

splenectomy had apparently alleviated the hemolytic process. Target cells were 5 to 20%. Reticulocytes, marrow hyperplasia, and hemolytic indices reflected a severe hemolytic process. The hemoglobin contained 60 to 80% type E hemoglobin.[639d]

Thalassemia. Thalassemia is not characterized by the production of an abnormal hemoglobin but is a manifestation of an inherited abnormality in hemoglobin metabolism.[633] Biochemical studies suggest that a partial block to normal adult hemoglobin synthesis is present [644] and that fetal hemoglobin is formed by reactivation of an embryonic mechanism.[633] Thalassemia, previously thought to occur only in persons of Mediterranean descent,¶ has been reported in Negroes.[657] During the preparation of this review, Minnich and co-workers published an excellent study of 32 cases of thalassemia major occurring in Thailand. Although no reports have been published, this entity has been recognized in Thailand for at least 15 years.[658] A characteristic accumulation of iron in thalassemia similar to that observed in idiopathic hemochromatosis is emphasized. It is thought that the fibrosis is due to continued hypoxia and not to iron overload.[659] An acquired extracorpuscular defect was demonstrated in seven children with thalassemia major, and splenectomy was found to be of value in four of five of these cases.[660]

Several cases of thalassemia-hemoglobin C disease have been reported.#

Sickle Cell Disease. Sickle cell syndrome may appear as the homozygous form,[322] as sickle cell-hemoglobin C disease, as sickle cell-hemoglobin D disease, or as sickle cell-thalassemia disease.*

Sickle cell-hemoglobin C disease has been reported several times † and appears to run a milder clinical course than sickle cell disease,‡ although splenomegaly is associated with it.§ The number of target cells (40 to 85%) is a distinctive feature of sickle cell-hemoglobin C disease and can be used to differentiate this condition from thalassemia or sickle cell disease.[653] A quantitative relationship in hemoglobin inheritance was observed in a family in which the mother had homozygous hemoglobin C, the father had sickle cell trait, one child had sickle cell-hemoglobin D disease, and two siblings had hemoglobin C trait.[652]

Sickle cell-hemoglobin D disease, the symptoms of which closely resemble sickle cell disease, has been observed in two Caucasian siblings.[634]

Sickle cell-thalassemia disease is thought to account for the majority of sickle cell disease cases in Caucasian persons.|| Sickle cell hemoglobin is the predominant type of hemoglobin in this disease, although fetal and normal adult hemoglobins are also present.[644]

1. Incidence. A summary of many studies conducted in Africa reveals a 20% frequency of the sickling phenomenon in a broad belt across the middle third of this continent.[634] Although the train occurs frequently, there is a paucity of sickle cell anemia reported from that area.¶ Sickling incidence in the Accra District of

¶ References 322 and 656.
* References 634, 635, 644, and 662.
† References 634, 635, 644, 652, 653, and 662.
# References 653 and 661.
‡ References 655 and 663.
§ References 641 and 663.
|| References 634 and 644.
¶ References 322 and 634.

the Gold Coast has been found to be 18.1%, and the calculated incidence (1%) of sickle cell anemia is thought to be correct.[664] Neel reviews the population dynamics of this disease and concludes that no significant difference exists between arbitrarily established ethnic ratings of individuals and the incidence of sickle cell disease.[665] In a study of sickling in Oriental Jews, Dreyfuss and co-workers[666] assume a genetic reservoir of sickling gene independent of Africa and associated with the Mediterranean area and race. In light of the high incidence of sickle cell anemia and trait in Petromagula and other foci in Greece, it is suggested that the sickle cell trait entered Africa by way of Neddisian blood from India.[667]

2. Clinical Aspects. Sickle cell disease is recognized by the characteristic findings of anemia, jaundice, thromboses, leg ulcers, variable sites of pain, low-grade fever, and sickled erythrocytes.# Intravascular sickling may be precipitated in the patient with sickle cell anemia by other disease processes.[669] Central nervous system involvement is relatively common and is manifested by drowsiness, stupor or coma, headaches, vomiting, irritability, and convulsions.[670] Impairment of urinary concentration has been noted in patients with sickle cell anemia.* Little is known about "pitressin-resistance," but it was postulated that renal tubular dysfunction is present. Hemodynamic studies of 13 patients with sickle cell anemia disclosed systolic murmurs in all cases and low arterial oxygen saturation in all but 1 case.[673]

3. Diagnostic and Physicochemical Aspects. Effective diagnosis of sickle cell disease by the moist stasis method should be controlled for false positive tests.[674] Wet marrow films are of value in the examination of children for preclinical sickle cell anemia.[675]

The ability of hemoglobin S to gel is influenced by various media and the accompanying types of hemoglobin.†

Hemoglobins A, S, and C have been differentiated by paper electrophoresis, a convenient, inexpensive, and accurate method.‡ This method is adequate for clinical, genetic, and anthropologic hemoglobin studies when used with the alkali denaturation technique.[682] Sickle cell hemoglobin has been identified by electrophoretic studies even when sickling cannot be induced by decreased oxygen tension.[683]

Red cell survival in abnormal hemoglobin conditions correlates well with severity of the hemolytic process.[684]

There is a significant difference in antigenic specificity between fetal and normal adult hemoglobins§ and small differences between sickle cell and normal adult hemoglobin.[685]

The sickling phenomenon has been shown to be the result of pseudocrystalline aggregates or tactoid formation of the sickle hemoglobin under decreased oxygen tension.|| Bar-like massing, aggregation, and tactoid formation have been observed tridimensionally by electron microscopy.¶ The age of the patient has no influence on sickling.[668] In the deoxygenated state, however, the potassium equilibrium of the sickle cell erythrocyte is disrupted and sodium rapidly enters the cell.[689] Optical

References 307-309 and 668.
* References 671 and 672.
† References 322 and 676.
‡ References 663 and 677-681.
§ References 649 and 685.
|| References 634, 686, and 687.
¶ References 687 and 688.

anisotrophy is present in sickle cells but not in thalassemic erythrocytes.[690] Sequestration of sickle cell anemia erythrocytes, but not of sickle cell trait cells, has been observed in the spleen.[621]

4. Complications. Pregnancy in sickle cell anemia has been reviewed.* Maternal mortality is 20 to 23%; fetal death rate is estimated to be as high as 43.2%.

Sickle cell trait predisposes Negroes to an acute exudative form of pulmonary tuberculosis but does not influence response to therapy for the infectious disease.[691] Sickle cell anemia has been associated with acute myeloblastic leukemia,[692] organic mitral stenosis,[693] and swelling of the distal extremities and unusual bone changes in an infant.[694] Similarities exist between the bone lesions of sickle cell anemia and bacterial osteomyelitis.[695] Homozygous hemoglobin C disease has been found in a case of cholelithiasis.†

5. Treatment. Corticotropin was beneficial in a case of sickle cell anemia in crisis.[696] Cobaltous chloride has little or no beneficial effect.[697] Benzazoline (Priscoline) has been used for relief of pain, with good results.[698] Treatment of patients with neurological manifestations by blood transfusions, sedation, oxygen, analgesics, and physical therapy has been suggested.‡

* References 307-310.

† References 652 and 654.

‡ References 308 and 670.

(To be continued)

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(To be continued)

Case Reports

ANTIBIOTIC TREATMENT OF BACTERIAL ENDOCARDITIS DUE TO ENTEROCOCCUS

Presentation of a Case and in Vitro Studies That Show a Potentiating Effect of Erythromycin, Chlortetracycline, and Streptomycin on Some Strains of Enterococci

BURTON ARMIN WAISBREN, M.S., M.D.
MILWAUKEE

THE EXCELLENT studies of Hunter,[1] Robbins and Tompsett,[2] and Cates, Christie, and Garrod[3] have established that the combination of penicillin and streptomycin is an effective treatment for most cases of bacterial endocarditis due to Enterococcus (Streptococcus faecalis, Group D Streptococcus). However, since all cases of enterococcal endocarditis do not respond to these antibiotics,* this report concerns a case that was cured with the combination of erythromycin, chlortetracycline, and streptomycin. These antibiotics were selected on the basis of in vitro studies of the causative bacteria. Data showing that erythromycin, chlortetracycline, and streptomycin are effective against other strains of enterococci also are presented. It is suggested on the basis of these findings that if penicillin and streptomycin are not effective in a case of enterococcal endocarditis, the combination of erythromycin, chlortetracycline, and streptomycin might be of value.

REPORT OF A CASE

The patient was a 27-year-old white married woman who entered the hospital with chills and fever. Before admission a blood culture revealed an Enterococcus. Her illness probably started about three months prior to admission, when she began to feel "below par," had a low-grade fever, and lost weight. Ten days before admission she developed a shaking chill, which was followed by a temperature of 104 F. She then consulted her physician, who administered a daily injection of penicillin and erythromycin by mouth for one week. In spite of this she continued to have a daily chill and fever. The positive blood culture was obtained three days before admission.

The pertinent points in her past history were that she was known to have had a heart murmur for 17 years; she disclaimed rheumatic fever; she had lost 20 lb. (9 kg.) in the past three months, and she had had extensive dental work without prophylactic penicillin five months before admission. She had no symptoms referable to her cardiovascular system and had been able to do her housework until 10 days before admission.

Physical examination revealed a chronically ill appearing young woman with *café-au-lait* complexion. Pertinent findings were as follows: Temperature, 98.6 F.†; pulse rate, 88 per minute; respiration rate, 18 per minute; blood pressure, 120/80; there were a few crepitant rales at the base of the right lung posteriorly; the heart appeared within the upper limits of normal in size; a presystolic murmur and a systolic murmur were heard at the apex; there was also a systolic murmur heard in the aortic area; the spleen was not palpable; the fingers were not clubbed; no petechiae, Osler's nodes, Janeway spots, or splinter hemorrhages were noted.

Laboratory data were as follows: red cell count, 3,700,000 per cubic millimeter; white cell count, 6,900 per cubic millimeter, with 84% polymorphonuclear leucocytes; the blood

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From the Infectious Disease Control Unit, Department of Medicine, Milwaukee County General Hospital, and Department of Medicine, Marquette University School of Medicine.

* References 2 and 3.

† All temperatures recorded in this report were oral.

Wassermann test, negative; urine specific gravity, 1.027; albumin, 1+; sugar, absent; no cellular elements seen on microscopic examination; electrocardiogram, normal; chest x-ray showed a normal-sized heart, with a "mitral" configuration. Studies on the Enterococcus isolated on admission showed the following bacteriostatic sensitivities to antibiotics: erythromycin, 0.39 γ per milliliter; penicillin, 3.12 units per milliliter; penicillin and erythromycin combined, 0.39 units of penicillin and 0.39 γ per milliliter of erythromycin.

The initial therapy consisted of 3,000,000 units of aqueous penicillin, given intravenously twice daily in 1 liter of 5% dextrose in water, and 100 mg. of erythromycin, given by mouth every six hours. During the first five days in the hospital the patient remained afebrile, but on the sixth day she began to have a daily fever (temperature of 100 F.). A blood culture at this time was sterile. In spite of a continual low-grade fever there appeared to be clinical improvement, and on the 15th hospital day the erythromycin was discontinued. On the 18th hospital day the temperature rose to 101 F., and on the 19th hospital day, to 102 F. Two blood cultures drawn at this time each grew enterococci. As a result of this, erythromycin was begun again, with a dosage of 400 mg. given orally every four hours. In spite of this the temperature each day continued to reach 101 F. The penicillin was discontinued on the 25th day, with a total dose of 150,000,000 units having been administered. The erythromycin was continued until the 36th hospital day, when it was discontinued, with a total dose of 36.2 gm. having been administered by mouth. A blood culture drawn on the 38th hospital day again grew enterococci. At this time an x-ray of the chest showed that significant enlargement of the heart had occurred since admission. In addition, the patient began to show signs of heart failure, and so she was digitalized and then kept on a maintenance dose of digitalis leaf. However, there was no evidence of emboli and the spleen was not palpable. Her fever, which had been becoming less intense, returned as soon as the erythromycin by mouth was stopped; therefore, on the 46th hospital day, the oral administration of 100 mg. of erythromycin every six hours was begun. After five days of this therapy she became afebrile.

On the 47th hospital day the patient was first seen by me. At this time the physical examination revealed a *café au lait* complexion and the previously described murmurs at the apex and base of the heart. A blood culture again grew enterococci. The patient was afebrile, and her spleen was not palpable.

Laboratory studies were as follows: hemoglobin, 12 gm.; white blood cell count, 9,900, with 76% polymorphonuclear leucocytes; no histiocytes were seen on the smear of the peripheral blood; nonprotein nitrogen concentration was 31 mg. per 100 cc.; sedimentation rate was 47 mm. in an hour (Westergren). While laboratory studies of the last organism isolated from the patient's blood were being done, 1 gm. of erythromycin was administered intravenously each day.

The tube-dilution test for determining the sensitivity of the bacteria to the various antibiotics[7] revealed that the combination of erythromycin and chlortetracycline was the most active (Table 1). In addition, this combination of antibiotics was shown to have a potentiating action when they were administered simultaneously to the patient (Table 2). Therefore, the dosage of erythromycin was increased to 1 gm., given intravenously in 150 ml. of 5% dextrose in water, twice per day, and 0.5 gm. of chlortetracycline was given by mouth every six hours. This combination of erythromycin and chlortetracycline was begun on the 51st hospital day. The patient was afebrile for the remainder of her hospital stay. However, blood cultures drawn on the 56th and 58th hospital days grew enterococci, and the sedimentation rate remained at 40 mm. in an hour. A blood culture drawn on the 61st hospital day remained sterile, but the sedimentation rate was still 37 mm. in an hour. Additional laboratory studies done at this time revealed that the bactericidal end-point in the antibiotic sensitivity test could be lowered by the addition of streptomycin (Table 1). For this reason and because the sedimentation rate was still elevated, the administration of 0.5 gm. of streptomycin intramuscularly twice per day was begun. Four days later the sedimentation rate fell to 23 mm. in an hour.

The chlortetracycline and erythromycin were administered for a total of 36 days, and during the last 21 days of this period streptomycin was also given. By the time chemotherapy was discontinued the patient was much improved and had been afebrile for 35 days. The heart murmur was unchanged, and her spleen was not palpable.

Laboratory studies were as follows: hemoglobin, 12.5 mg. per 100 cc.; white blood cell count 8,900, with 59% polymorphonuclear leucocytes; sedimentation rate 31 mm. in an hour; nonprotein nitrogen, 32 mg. per 100 cc.; urinalysis showed specific gravity of 1.020, 1+ albumin, and three to four white blood cells per high-power microscopic field. Four blood cultures drawn after cessation of therapy remained sterile.

Since discharge from the hospital, on June 20, 1953, the patient has been maintained on digitalis and diuretics. She was afebrile until six months after discharge, when she had an acute onset of chills, fever, chest pain, and hemoptysis. A presumptive diagnosis of pulmonary infarction was made, and there was an excellent response to penicillin and bed rest. Three

TABLE 1.—*Results of Sensitivity Tests on the Enterococcus Isolated From the Patient*

Antibiotic	Concentration Necessary to Inhibit Organism,† γ/Ml.	Concentration Necessary to Kill Organism,† γ/Ml.
Chlortetracycline	1.5	..
Oxytetracycline	3.0	..
Penicillin	3.0	25
Streptomycin	100.0	>100
Erythromycin	1.5	6
Chlortetracycline and erythromycin *	0.19	6
Erythromycin and penicillin	1.5	6
Penicillin and streptomycin	3.0	3
Erythromycin and streptomycin	3.0	6
Chlortetracycline, erythromycin, and streptomycin	0.19	2.25
Chlortetracycline and streptomycin	3.0	..

* In the combinations the figures represent the amount of each antibiotic used; i. e., inhibition was obtained with a solution containing 0.19 γ per milliliter of chlortetracycline and 0.19 γ per milliliter of erythromycin, or a total of 0.38 γ per milliliter of drug.

TABLE 2.—*"In Vivo" Studies on the Results of Giving Combination of Erythromycin and Chlortetracycline to the Patient**

Drug	Dose, Gm.	Route	Dilution of Serum Necessary to Inhibit Enterococcus Isolated from the Patient
Erythromycin	1	Intravenous	1:4
Chlortetracycline	0.5	Oral	1:2
Erythromycin	1	Intravenous	...
Chlortetracycline	0.5	Oral	1:16

* On the first day of this study, erythromycin was administered by vein to the patient. One-half hour later her blood was drawn and a determination made of the dilution of her serum that would inhibit the growth of a 1:100 dilution of an 18-hour growth of the enterococci that had been initially grown from her blood. On the second day the experiment was repeated one-half hour after chlortetracycline was given, and on the third day the bacteriostatic potency of her blood was determined one-half hour after the chlortetracycline had been given by mouth and the erythromycin by vein. Bactericidal studies in each case revealed that in spite of the inhibition the organisms were still viable in the undiluted serum.

blood cultures taken before the penicillin was administered were sterile. One year after discharge from the hospital the patient had shown no evidence of recurrence of the endocarditis but still required care for congestive failure.

COMMENT AND PRESENTATION OF ADDITIONAL IN VITRO STUDIES

Since neither chlortetracycline, erythromycin, nor streptomycin has been generally accepted as effective in the treatment of bacterial endocarditis,‡ their effectiveness when combined is somewhat surprising. This finding emphasizes the clinical

‡ References 4-6.

truism that when the patient is not responding every therapeutic possibility must be investigated, regardless of theoretical considerations. In a case such as this, in which there is a persistent, rapidly growing organism, in vitro studies serve a particularly useful function, because many possible therapeutic regimens may be tried in vitro before the patient is subjected to therapy that has little chance of success. Viewed in this light, the extensive laboratory work that was necessary in this case proved an economy.

Why therapy with the combination of penicillin and streptomycin was not begun before erythromycin and chlortetracycline were administered is a logical question. The reason for this was that the organism was more resistant in vitro than were the organisms in most of the cases that had been published.§ If the erythromycin and chloramphenicol had been ineffective, penicillin and streptomycin would have been the next agents used. If investigative considerations would have been primary, the patient would have been given a course of chlortetracycline to establish the fact

TABLE 3.—*Results of the Tube-Dilution Test of the Bacteriostatic Activity of Chlortetracycline, Streptomycin, and Erythromycin Used Alone and in Combination Against Five Cultures of Pathogenic Enterococci*

Culture No.	Bacteriostatic Inhibitory Concentration,* γ/Ml.					Results of Combining the Antibiotics †			
	C *	S	E	CS	ES	CS	ES	CE	CES
1	6	100	1.5	25‡	1.5	I	A	A	P
2	0.19	6	1.5	0.38	3	N	N	A	A
3	12	100	6	6	3	A	P	A	A
4	0.38	12	0.75	1.5	0.75	I	A	A	P
5	3	100	1.5	6	1.5	N	A	N	N

* C, chlortetracycline; S, streptomycin; E, erythromycin; CS, chlortetracycline and streptomycin; ES, erythromycin and streptomycin.

† A, additive effect, i. e., total amount of drug necessary for inhibition is the same but is made up of two antibiotics instead of one; N, no effect, i. e., the addition of a second antibiotic did not change the amount of the most effective antibiotic that was needed for inhibition; P, potentiation, i. e., less total antibiotic was needed for inhibition when a combination was used; I, inhibition, i. e., more of the most effective antibiotic was needed when a second antibiotic was added. See Figure 1 for actual data for CE and CES.

‡ An end-point of 25 means that 12.5 γ of each drug was necessary for inhibition.

that this drug given alone was not curative. However, in view of the record of this agent when used alone in bacterial endocarditis, such a course of therapy was not justified.[5]

Similarly, it was not established whether or not the addition of streptomycin was necessary for cure, but it was felt, on the basis of the in vitro studies, that the drug should be added even though it would complicate a scientific appraisal of the end-result. The fact that a 1 : 16 dilution of the patient's serum inhibited the organism after erythromycin and chlortetracycline had been given and that a 1 : 4 dilution was necessary when each of these drugs was given individually was evidence that the potentiation observed in vitro also occurred when the drugs were given to the patient (Table 2).

The in vitro and clinical results herein reported stimulated a brief study in which five other strains of enterococci were tested to see if these in vitro findings could be repeated. In this study five other strains of enterococci that had been isolated from infections were tested for their sensitivity to erythromycin, chlortetracycline, strepto-

§ References 2 and 3.

mycin, and penicillin used alone and in various combinations. The tube-dilution method was used, and in each case bactericidal as well as bacteriostatic end-points were determined.[7]

The results of the bacteriostatic studies are presented in Table 3 and Figure 1. In two of the five cultures the combination of erythromycin, chlortetracycline, and streptomycin resulted in potentiation of the bacteriostatic activity (Fig. 1, Cultures 1 and 4). In Cultures 2 and 3 an additive effect was demonstrated, and in Culture 5 the addition of streptomycin did not decrease the activity of the chlortetracycline

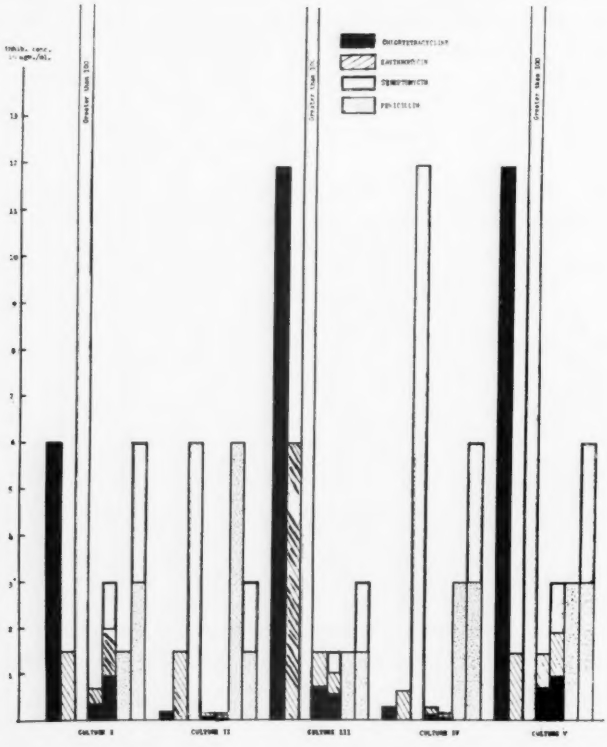

Fig. 1.—The bacteriostatic activity of various antibiotics used alone and in combination against five cultures of pathogenic enterococci. The tube-dilution test was used.[7]

and erythromycin. The results of tests of the other possible combinations are shown in Table 3. These findings show that in specific instances potentiation, additive effects, and inhibition may occur when combinations are used. In no cases were the combinations of chlortetracycline and streptomycin or of erythromycin and streptomycin more bacteriostatic than the combination of chlortetracycline and erythromycin (Table 3; Fig. 1). It is of importance also to note that in each of the five cultures the combinations of chlortetracycline and erythromycin, both with and without streptomycin, were more effective than the combination of penicillin and streptomycin.

In the bactericidal studies the superiority of chlortetracycline, erythromycin, and streptomycin was not as marked. In two instances (Cultures 2 and 4) penicillin and streptomycin were superior (Fig. 2). The three other cultures were killed by less chlortetracycline, erythromycin, and streptomycin than was necessary when the combination of penicillin and streptomycin was used (Figure 2; Cultures 1, 3, and 5). In no case did the combining of the agents lead to inhibition of bactericidal activity (Table 4).

These results in toto show that the combination of erythromycin and chlortetracycline and the combination of erythromycin, chlortetracycline, and streptomycin

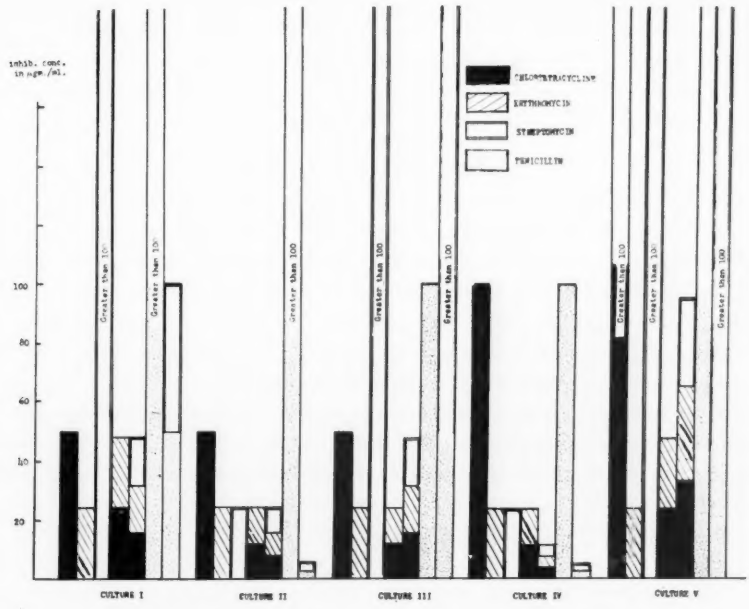

Fig. 2.—The bactericidal activity of various antibiotics used alone and in combination against five cultures of pathogenic enterococci. A modification of the tube-dilution test was used.[7]

TABLE 4.—*Results of the Tube-Dilution Test of the Bactericidal Activity of Chlortetracycline, Streptomycin, and Erythromycin Used Alone and in Combination Against Five Cultures of Pathogenic Enterococci*

Culture No.	Bactericidal Inhibitory Concentration, γ/Ml.					Result of Combining the Antibiotics *			
	C *	S	E	CS	ES	CS	ES	CE †	CES †
1	50	>100	25	50‡	50	A*	N	P	A
2	50	25	25	25	6	A	P	A	A
3	50	>100	25	50	50	A	N	P	N
4	100	25	25	25	6	A	P	A	P
5	>120	100	25	200	50	N	N	A	N

* See Table 3 for abbreviations.
† See Figure 2 for the actual data.
‡ The value 50 represents a concentration of 25 γ per milliliter of each antibiotic.

may show bacteriostatic and bactericidal additive and potentiating activity against enterococci. In all six cultures tested these drugs were bacteriostatic in lower concentration than was necessary when penicillin and streptomycin were used. In three cultures they were also more bactericidal than penicillin and streptomycin.

The excellent clinical results achieved with penicillin and streptomycin in cases of enterococcal endocarditis make these agents the drugs of choice in this condition. On the other hand, this case report and in vitro study make the combination of erythromycin, chlortetracycline, and streptomycin a reasonable one for use in cases that do not respond to penicillin and streptomycin. In fact, subsequent to these studies we have successfully treated three cases of bacterial endocarditis with chlortetracycline and erythromycin after they had failed to respond to penicillin and streptomycin. In one the offending organism was viridans Streptococcus, and in the other two no positive blood cultures were obtained. Jones and Yow [8] also have reported the successful treatment with erythromycin and streptomycin of a case of bacterial endocarditis due to viridans Streptococcus.

SUMMARY AND CONCLUSIONS

A case of bacterial endocarditis due to an Enterococcus was treated successfully with a combination of erythromycin, chlortetracycline, and streptomycin. This combination was found in vivo and in vitro to exhibit bacteriostatic potentiation and a bactericidal additive effect against the causative strain of Enterococcus.

This combination of antibiotics was more bacteriostatic than penicillin and streptomycin in five other strains of enterococci. It was also more bactericidal than penicillin and streptomycin against three of these five strains.

These results suggest that when a case of bacterial endocarditis due to enterococcus does not respond to penicillin and streptomycin the combination of erythromycin and chlortetracycline or of erythromycin, chlortetracycline, and streptomycin might be of benefit.

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BILLINGS
Silver Medal
FOR CORRELATION AND PRESENTATION OF FACTS

THE SCIENTIFIC EXHIBIT
AMERICAN MEDICAL ASSOCIATION
SAN FRANCISCO – 1954

PORTAL HYPERTENSION

DONALD C. BALFOUR Jr., M.D.
TELFER B. REYNOLDS, M.D.
WILLIAM P. MIKKELSEN, M.D.
ARTHUR C. PATTISON, M.D.
AND
MILTON R. HALES, M.D.
LOS ANGELES

THE EXHIBIT approaches the problem of portal hypertension by presenting normal and cirrhotic comparative data in the field of pathology (M. R. H.), internal medicine (D. C. B. and T. B. R.), and surgery (A. C. P. and W. P. M.). The possible physiological factors involved in causing the elevation of portal pressure are demonstrated. The clinical determination of portal pressure, care of emergency bleeding, and surgical treatment as done at this institution are summarized.

Gross Vascular Anatomy of Liver.—Figures 4, 5, and 6 illustrate vinylite corrosion casts of the vascular systems of

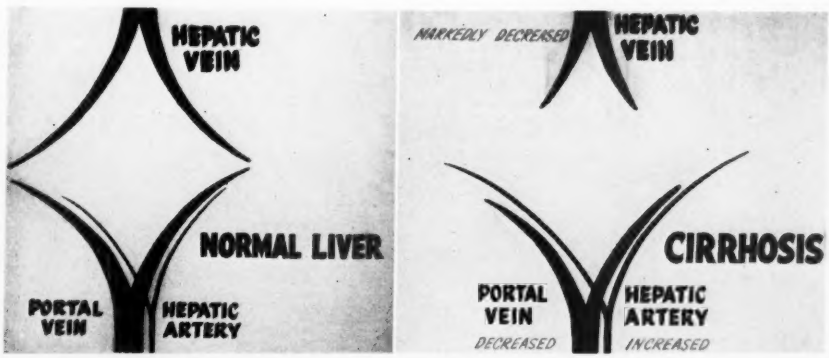


Fig. 3.—Diagrammatic representation of the extent of vascular injection in the vinylite casts of normal and cirrhotic livers. The original charts were colored to correspond to the color of the plastic injected into the liver specimens. Hepatic vein, yellow; portal vein, red, and hepatic artery, black.

From the University of Southern California School of Medicine, Departments of Medicine, Surgery, and Pathology, and the Los Angeles County Hospital; Assistant Clinical Professor of Medicine (Dr. Balfour), Assistant Professor of Medicine (Dr. Reynolds), Instructor in Surgery (Dr. Mikkelsen), Associate Clinical Professor of Surgery (Dr. Pattison), and Assistant Professor of Pathology (Dr. Hales).

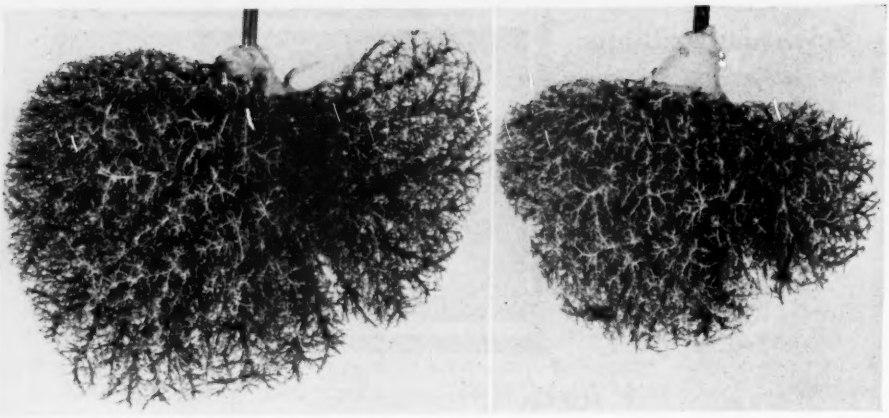


Figure 4

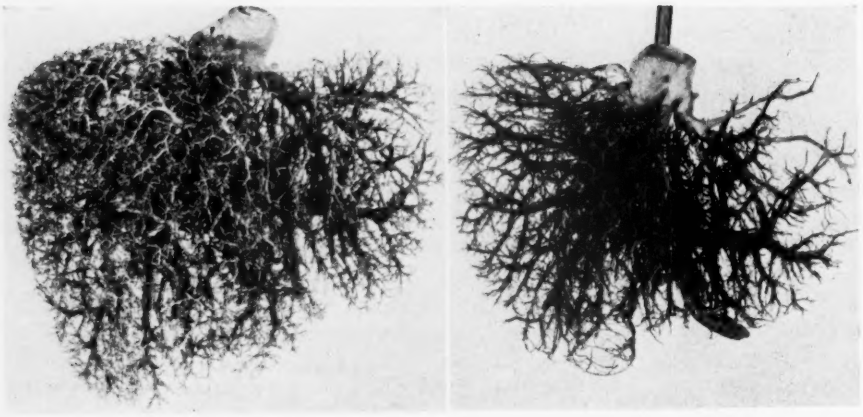


Figure 5

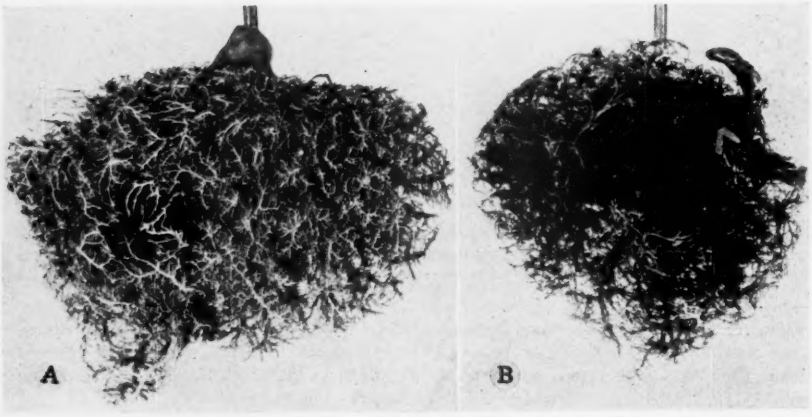


Figure 6

normal, cirrhotic, and tumor-bearing livers. In the preparation of such specimens, acid-resistant colored vinylite solutions are injected into the vessels; after the plastic has solidified the surrounding tissue is digested away.

In the two normal livers shown in Figure 4 there is an equal and uniform injection of the hepatic and portal venous systems. In black and white illustrations these appear, respectively, light and dark gray. Hepatic arterial injection (black) is small. Figure 5 shows two cirrhotic livers. Here the hepatic arterial system (black) is increased, while the hepatic and portal venous systems are decreased. In most cirrhotic livers studied there has been a greater reduction in the hepatic venous system than in the portal venous system. Although the hepatic arterial injection fills vessels as small as 150 μ, no arteriovenous anastomoses have been demonstrated.

Figure 6, left, shows the hepatic metastases of a very vascular renal carcinoma with a rich hepatic arterial supply (black). On the right is shown a hepatoma in which the arterial bed is extensive, while the veins have been obliterated.

Circulatory Physiology.—To demonstrate all possible factors causing portal hypertension, a constant-pressure pump circulates fluid through the simulated splanchnic bed and liver. Rates of flow can be changed by the valves to simulate the changing conditions associated with cirrhosis and portal hypertension.

Figure 7 *A* shows normal rate of flow and free flow through the liver. A normal pressure of 5 to 10 mm. Hg is represented in the column at the left, and relatively slight overflow can be seen through perforations in the side of this column. This represents collaterals such as esophageal varices, which cannot be seen in these photographs.

Figure 7 *B*. Partial closure of the valve at (*1*) represents obstruction of flow through the liver.

It is well known that flow of blood through the liver is decreased in cirrhosis. The model shows elevation of pressure to about 15 mm. Hg by this partial obstruction.

Figure 7 *C*. Are other hydrodynamic factors influential? Because of the fact that (*a*) when liver disease is not present ligation of the portal vein with complete obstruction causes little significant permanent portal hypertension and (*b*) we have failed to demonstrate retrograde flow in the portal vein at operation, increased inflow must be considered.

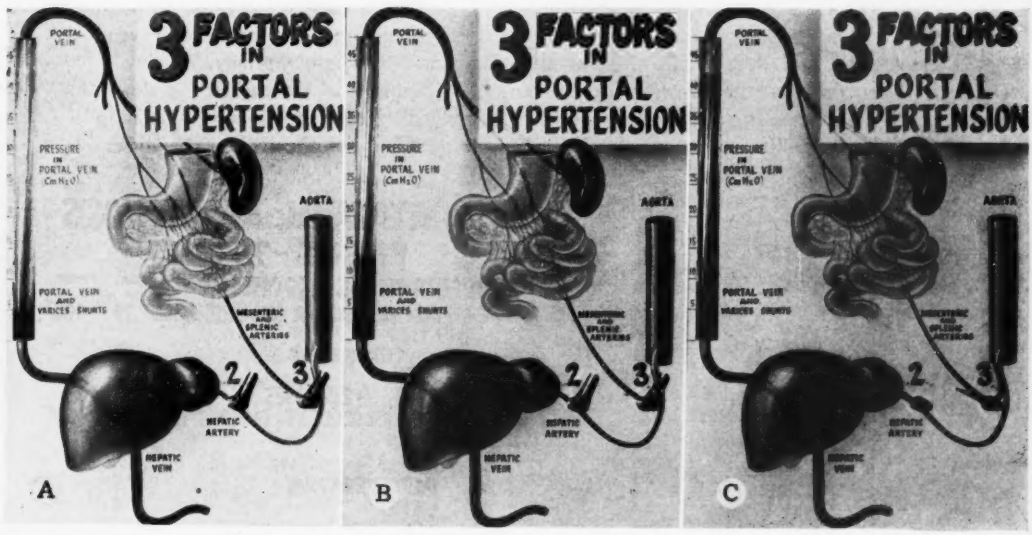


Figure 7

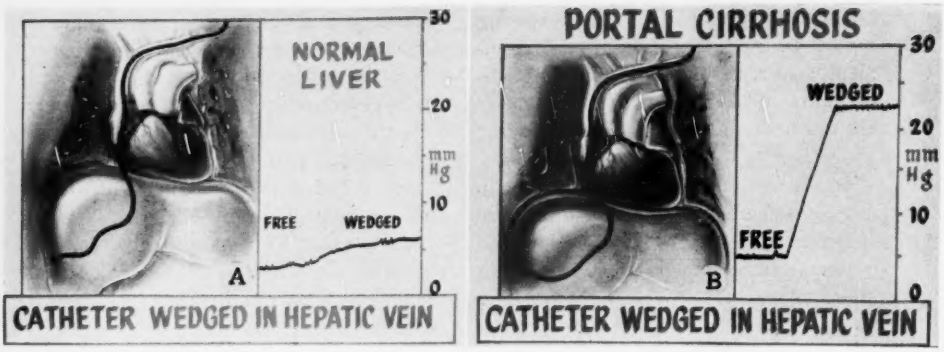
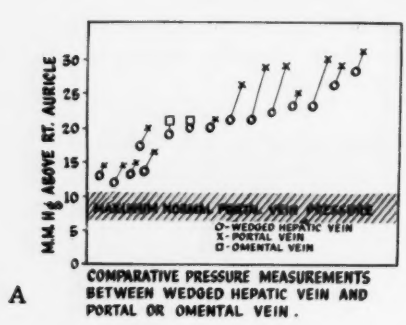


Figure 8



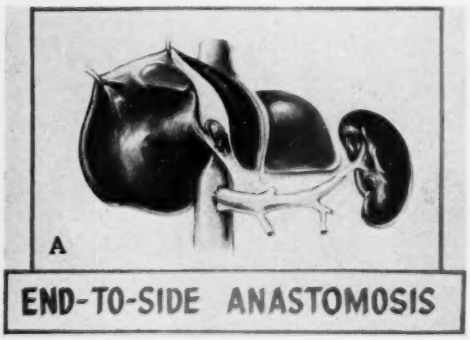
DIAGNOSIS	NO. OF CASES	WEDGED HEPATIC VEIN PRESSURE (mm Hg above rt. auricle) MEAN AND RANGE
WITHOUT LIVER DISEASE	27	6.0 (3.6 - 11.0)
CIRRHOSIS		
ALCOHOLIC	50	22.3 (12.0 - 38.0)
XANTHOMATOUS BILIARY	2	16.5 (14 - 19)
HEMOCHROMATOSIS	3	15.8 (14 - 18)
POST-HEPATITIC	1	24
BILIARY	1	10
EXTRA-HEPATIC PORTAL HYPERTENSION	4	7.5 (4.3 - 11)
OBSTRUCTIVE JAUNDICE	10	6.2 (2.0 - 12.3)
VIRAL HEPATITIS	4	10.5 (9.0 - 12.5) B

Figure 9

On the model, increasing flow of (*2*) and/or (*3*) causes pressure to be elevated to higher levels, as seen in cirrhosis. The increased size of the hepatic arterial system, as shown in the injection specimens, could mean increased pressure and flow. Inflammation and obstruction in the liver, with reflex arterial dilatation, could cause increase in flow into the entire splanchnic bed.

Clinical Measurement of Portal Pressure.—Portal venous pressure can be measured indirectly by catheterization of a hepatic vein. This is accomplished by passing a cardiac catheter through the right atrium into the inferior vena cava and then into the hepatic vein.

In Figure 8 *A* the catheter is shown "wedged" into a small hepatic vein in the periphery of the liver. The differ-



PORTACAVAL ANASTOMOSIS
RESULTS - 75 CASES

	CASES	PERCENT.
HEMORRHAGE (49 CASES)		
LIVING, NO FURTHER HEMORRHAGES	39	79.6%
DEATHS		
POSTOPERATIVE	4	
LATE	6	
ASCITES (26 CASES)		
NO SUBSEQUENT FLUID	13	50%
FLUID	3	
DEATHS		
B POSTOPERATIVE	5	
LATE	5	

Figure 10

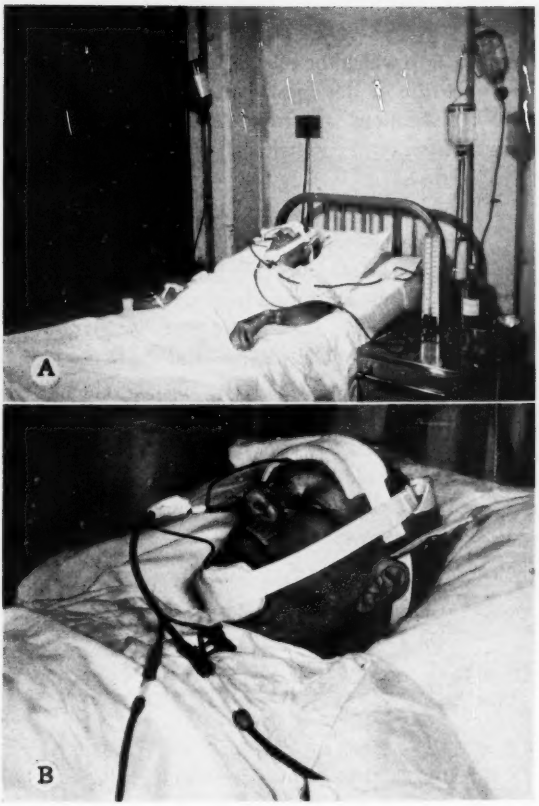


Figure 11

ence between "wedged" and "free" hepatic vein pressure is small in subjects without liver disease.

Figure 8 *B* shows how the "wedged" pressure is elevated in subjects with cirrhotic liver disease and there is an abrupt drop in pressure as the catheter is withdrawn from the wedged position to lie free in the hepatic vein.

Direct simultaneous comparisons have been made in patients with portal hypertension between the wedged hepatic vein pressure and the actual portal vein pressure measured at surgery.

Figure 9 *A* shows these results. There have been no major discrepancies, and the wedge pressure averages 20% below the true portal pressure.

In Figure 9 *B* it can be seen that cirrhotic liver disease of any type causes an elevation in the wedged hepatic vein pressure.

In normal persons, in noncirrhotic liver disease, and in extrahepatic portal hypertension no significant elevations in wedge pressure have been found.

Emergency Care of Bleeding Varices.—Active bleeding from esophageal varices has been almost always stopped by use of an esophageal tamponage balloon (Sengstaken-Blakemore) in our series of more than 100 treated cases. This balloon is also of great diagnostic aid when there is doubt as to the source of bleeding. If the aspiration of fresh blood ceases with the balloon in place, bleeding varices is most likely, whereas if fresh blood continues to appear, the bleeding is probably from the stomach or duodenum.

Surgical Treatment.—Figure 10 *A* shows the completed end-to-side portacaval anastomosis. There have been no observed ill effects from completely diverting the portal blood from the liver.

Figure 12

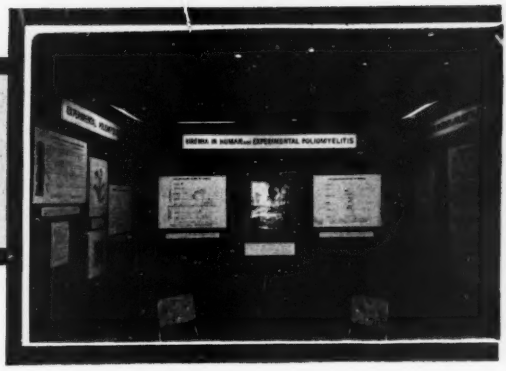
Figure 10 *B* shows the results obtained in 75 cases of end-to-side portacaval anastomoses for the relief of portal hypertension. Of great significance in the selection of patients for a shunt procedure, and particularly if the shunt is done for the relief of ascites alone, is the serum albumin concentration. This value should be above 3.0 gm. and preferably above 3.5 gm. per 100 cc. In the last 55 cases, the over-all mortality has been 9.1%.

Figure 11 *A* shows a patient with esophageal varices that have bled with the Sengstaken tube properly in place.

Figure 11 *B* shows a method of maintaining proper traction on the Sengstaken-Blakemore tube by use of a head mask to which the tube is taped securely. The use of this mask has avoided such complications as strangulation, loss of traction on the gastric balloon, and nose necrosis.

Figure 12 shows a splenoportogram done by injection of 70% acetrizoate (Urokon) into the spleen, with serial films begun at the midpoint of the injection. Here, the splenic vein is not visible, having been fibrosed at the site of an old pancreatitis. The splenic vein block has resulted in extensive gastric varices. Relief of this mechanical block of the splenic vein was accomplished by removal of part of the stomach and spleen en bloc.

Scientific Exhibits



VIREMIA IN HUMAN AND EXPERIMENTAL POLIOMYELITIS

DOROTHY M. HORSTMANN, M.D.
ROBERT W. McCOLLUM, M.D.
ANNE D. MASCOLA
AND
JOHN T. RIORDAN
NEW HAVEN, CONN.

THIS EXHIBIT presents evidence that in clinical poliomyelitis a systemic phase, which may be accompanied by symptoms of the minor illness or may be entirely asymptomatic, precedes involvement of the central nervous system. Only recently has it become apparent that, during the systemic infection, virus is present in the blood stream for several days. Chimpanzees and cynomolgus monkeys experimentally infected by a natural route, i. e., orally, have been shown to have viremia between the third and eighth days after virus ingestion. In the case of the cynomolgus monkey, this is during the incubation period, some days before the onset of paralysis. In experimental animals, viremia is followed by prompt and early appearance of antibodies, which have been found at the time of onset of signs of disease.

Community Epidemiology.—The spread of poliomyelitis through a community is better understood when it is realized that the majority of infections are inapparent or associated only with the minor illness. In order to demonstrate viremia in the human infection, it is necessary for the clinical investigator to go into homes, particularly those in which a frank infection has occurred, and to collect specimens from contacts who might be in the incubation period or minor illness phase of infection. Four of five children whose blood, throat, and rectal swabs were positive for virus were out playing the day after the positive specimens were obtained. Although the period of viremia is short, the children continue to excrete virus in the throat and feces for some time. Thus, in a community it is the well children, or those with the mild, brief, systemic form of the disease, who are the source of virus spread in this highly communicable infection.

From the Section of Preventive Medicine, Yale University School of Medicine.

Aided by a grant from the National Foundation for Infantile Paralysis.

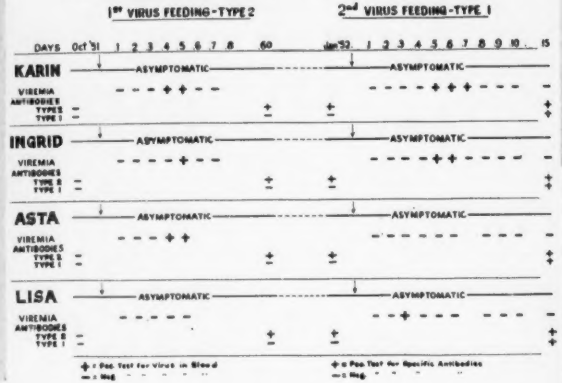
The New York Zoological Society provided the pictures of chimpanzees used in this exhibit.

EXPERIMENTAL POLIOMYELITIS

Four chimpanzees were infected orally (↓) on two occasions two and one-half months apart, with two different immunologic types of poliomyelitis virus. Each time, three of the four were demonstrated to have viremia, and all four developed type-specific antibodies.

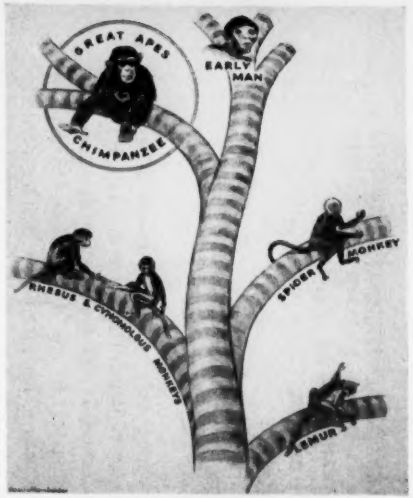
▼

VIREMIA IN CHIMPANZEES FED POLIOMYELITIS VIRUS



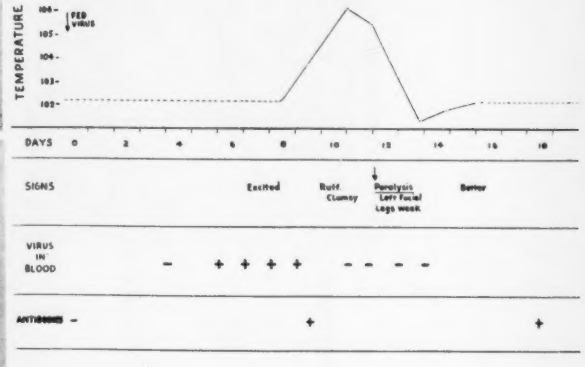
The "human" aspects of the attitudes and behavior of chimpanzees suggest their close relationship to man.

▶



◀ Chimpanzees are the closest to man on the phylogenetic tree. Like man, they usually respond to ingestion of poliomyelitis virus by developing an asymptomatic intestinal carrier state and specific immunity.

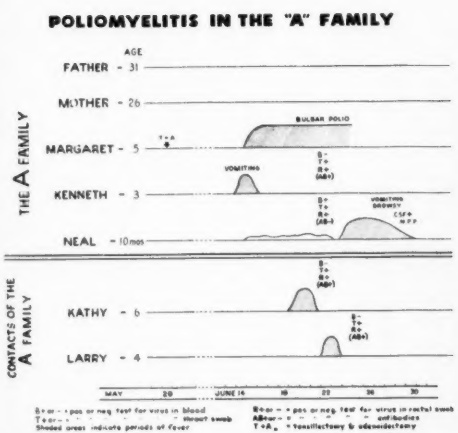
VIREMIA IN A CYNOMOLGUS MONKEY FED TYPE I VIRUS



▲

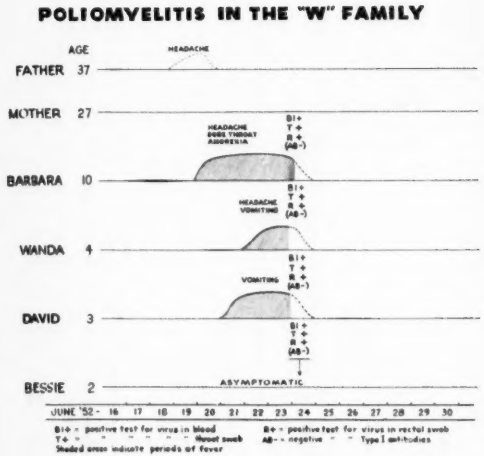
The above is typical of a number of cynomolgus monkeys which acquired paralytic poliomyelitis after ingestion of the virus and were shown to have viremia during the incubation period. Similar results have been obtained in animals given virus subcutaneously.

VIREMIA IN HUMAN POLIOMYELITIS

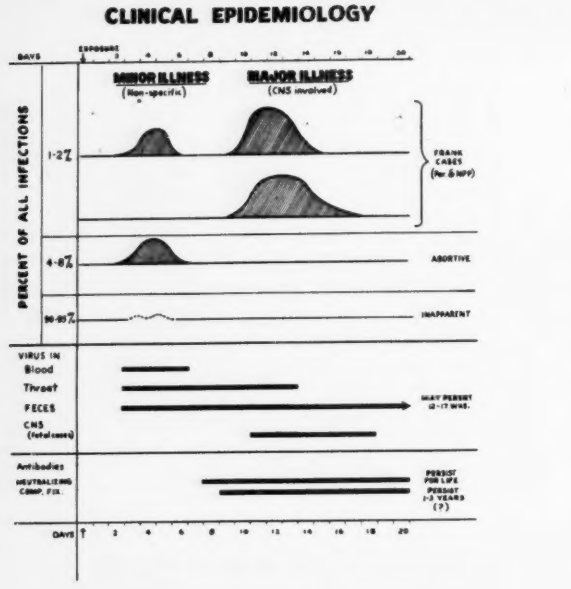


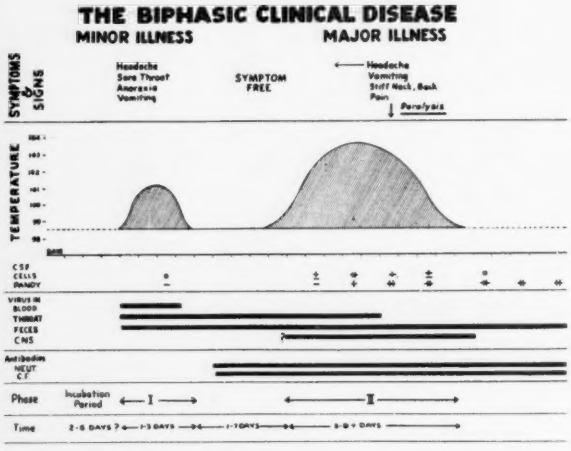
Type 1 virus was demonstrated in Neal's blood three days before the onset of mild nonparalytic poliomyelitis; virus was also present in his throat and rectal swabs. His brother Kenneth and two playmates had brief febrile episodes (minor illnesses) about the same time and were also infected with Type 1 poliomyelitis virus; however, their blood specimens already contained Type 1 antibodies and were therefore negative for virus.

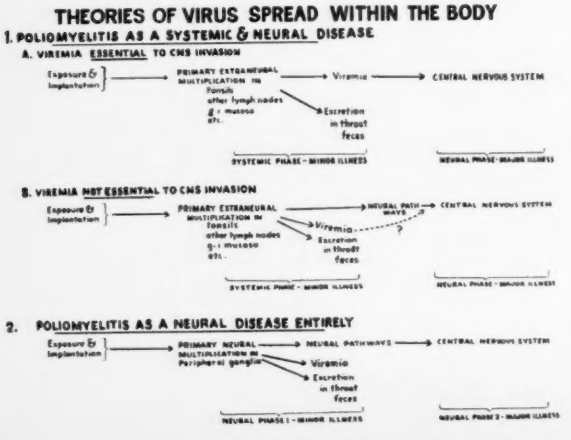
In the present study, specimens were collected from members of the "W" and the "A" families, who were similar to the children in this scene. The children shown above, although completely well, could have viremia and could excrete virus in the throat and feces for several weeks, thus serving as disseminators of the infection.



Type 1 poliomyelitis virus was isolated from blood, throat, and rectal swabs of all four children in the "W" family. Three of the children had the minor illness syndrome; one remained asymptomatic. None developed clinically apparent poliomyelitis—either paralytic or nonparalytic.






THEORIES OF VIRUS SPREAD WITHIN THE BODY
1. POLIOMYELITIS AS A SYSTEMIC & NEURAL DISEASE
A. VIREMIA ESSENTIAL TO CNS INVASION
Exposure & Implantation
PRIMARY EXTRANEURAL MULTIPLICATION IN Tonsils other lymph nodes G-I mucosa etc.
Viremia
CENTRAL NERVOUS SYSTEM
Excretion in throat feces
SYSTEMIC PHASE - MINOR ILLNESS
NEURAL PHASE - MAJOR ILLNESS
B. VIREMIA NOT ESSENTIAL TO CNS INVASION
Exposure & Implantation
PRIMARY EXTRANEURAL MULTIPLICATION IN tonsils other lymph nodes G-I mucosa etc.
NEURAL PATH WAYS
CENTRAL NERVOUS SYSTEM
Viremia
Excretion in throat feces
2. POLIOMYELITIS AS A NEURAL DISEASE ENTIRELY
Exposure & Implantation
PRIMARY NEURAL MULTIPLICATION IN Peripheral ganglia
NEURAL PATHWAYS
CENTRAL NERVOUS SYSTEM
Viremia
Excretion in throat feces
NEURAL PHASE I - MINOR ILLNESS
NEURAL PHASE II - MAJOR ILLNESS

NATURAL HISTORY OF POLIOMYELITIS

Nature of Poliomyelitis.—Regardless of whether a person has a completely inapparent infection or a severe paralytic one, the course of events is similar in terms of the establishment of infection, the localization of virus in extraneural sites, its presence in the throat, its excretion in the feces, and the appearance of antibodies and immunity. Viremia has been shown to occur during the minor illness, i. e., the first, or systemic, phase of the disease, but whether it is essential to central nervous system invasion has not yet been conclusively proved. In any event, there is increasing evidence that poliomyelitis is not a disease of the nervous system only, but an extremely common systemic infection, almost as contagious as measles.

Schematic diagrams, showing (1) The relative frequency of clinical and subclinical forms of poliomyelitis (shaded areas indicate periods of fever), (2) the presence of virus in various anatomic sites during the course of infection, and (3) the time at which antibodies appear.

Correspondence

TIMIDITY AND CAVEATS

The correspondence to which the following letters pertain relates to statements in an editorial by Dr. William B. Bean, in the July, 1954, issue of the A. M. A. ARCHIVES OF INTERNAL MEDICINE.

The particular statements referred to in Admiral Boone's letter follow:

"Reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration."

"Published with the approval of the Chief Medical Director of the Veterans Administration. The statements and conclusions published by the authors do not necessarily reflect the opinion or policy of the Veterans Administration."

It will be recalled that Dr. Bean was somewhat critical in his editorial of statements appearing with medical articles in which the organizations or institutions from which a given publication emanated made a point of disclaiming responsibility for what the author said.

P. S. R.

To the Editor:—My attention has been drawn to the editorial by Dr. Bean in the July issue of your Journal. I have read it with interest and find myself in general agreement with its thesis. I would, however, like to draw your attention to a factual error contained in the last two subparagraphs on page 2. The footnotes to which reference is there made have not been format in the Veterans Administration since January 4, 1952. The only footnote required subsequent to that time has been the customary one referring to the title and location of the author or authors.

I would appreciate it if you could find room to publish this correction in an early issue of your Journal.

Very sincerely yours,
J. T. BOONE
Vice Admiral (M.C.) U. S. Navy, Rtd.
Chief Medical Director

Nothing is so deflating as to have the rug pulled out from under you as the punch line is being delivered, if I may mix and mangle my metaphors. Admiral Boone was on the alert before my blast aroused his frown. Lest his very palpable touch pink me without ripost, I must attract his roving eye to the August number of the A. M. A. ARCHIVES OF INTERNAL MEDICINE where on page 264 the not yet completely submerged subscript raises its evil leer. Perhaps all this shows is that though the wheels of the Veterans Administration grind fine, they do indeed grind with marvelous slowness. Regardless of certain rather remarkable delays, the Veterans Administration at least has made a very proper step forward. I am sorry for any disservice I have done them in aiming at a target they have already made efforts to take down. It is great solace to me that we see eye to eye.

WILLIAM B. BEAN, M.D.

News and Comment

ANNOUNCEMENTS

National Foundation for Infantile Paralysis Fellowships.—The National Foundation for Infantile Paralysis announces the availability of a limited number of postdoctoral fellowships in medicine and the related biological sciences.

These fellowships are awarded as a part of the National Foundation's program of professional education, for which more than $19,000,000 in March of Dimes funds have been appropriated since 1938.

These fellowships are offered to candidates who are preparing for careers in scientific research and/or academic medicine. They are not awarded to investigators for the support of a research project. Special consideration will be given to applicants interested in such fields as microbiology, biochemistry, biophysics, orthopedics, pediatrics, neurology, and epidemiology.

Eligibility requirements include an M.D., Ph.D., or equivalent degree, United States citizenship (or application for citizenship), and sound health.

Selection of candidates will be made on a competitive basis by the National Foundation's Fellowship Committee. Fellowships will be awarded for a period of one to three years, and in rare instances they may be extended to five years.

Stipends ranging from $3,600 to $7,000 a year are allowed, the specific sum being determined by marital status and number of dependents. The institution in which the Fellow receives his training may request compensation of $500 to $1,000 a year.

For consideration by the Fellowship Committee in February, applications must be received by Dec. 1; for consideration in May, applications must be filed by March 1; for consideration in November, by Sept. 1.

For further information and application blanks address The National Foundation for Infantile Paralysis, Division of Professional Education, 120 Broadway, New York 5.

Bound Copies of Bulletin on Rheumatic Diseases Available to Physicians.—The first four volumes of the *Bulletin on Rheumatic Diseases* have been bound in soft cover and are now available to physicians.

The *Bulletin*, published by the Arthritis and Rheumatism Foundation, is issued nine times a year and is available without charge to all physicians and medical students who request it.

Physicians wishing to regularly receive the *Bulletin on Rheumatic Diseases*, at no cost, should write to Dr. Russell L. Cecil, Medical Director, Arthritis and Rheumatism Foundation, 23 West 45th St., New York 36.

The bound special volume, composed of all issues of the *Bulletin* of the past four years, is available from the Arthritis Foundation at the cost of $1.

The *Bulletin*, the only American publication in the field of the rheumatic diseases, was started in 1950 to foster greater interest in the rheumatic diseases among physicians. Its aim is to keep doctors abreast of the more important clinical advances and changing concepts of the rheumatic diseases promptly, simply, and succinctly.

Western Society for Clinical Research.—The eighth annual meeting of the Western Society for Clinical Research will be held Jan. 28 and 29, 1955, at Carmel, Calif.

Information regarding the meeting may be obtained from Herbert N. Hultgren, M.D., secretary-treasurer, Stanford Hospital, San Francisco 15.

NOTICE

The Annual Meeting of the American Medical Association will be held in Atlantic City, June 6-10, 1955. Physicians hoping to take part in that meeting should communicate with their Section officers as early as possible. Deadlines have been set, after which applications will be considered only if there are withdrawals in the program.

DEADLINE FOR SECTION PAPERS, Dec. 15, 1954

DEADLINE FOR SCIENTIFIC EXHIBIT, Jan. 10, 1955

Communications should be addressed to the following:

Section on Internal Medicine

Secretary—A. Carlton Ernstene, M.D., 2020 East 93rd St., Cleveland 6, Ohio

Representative to Scientific Exhibit—John S. Lawrence, M.D., 405 Hilgard Ave., Los Angeles 24, Calif.

Section on Experimental Medicine and Therapeutics

Secretary—George E. Burch, M.D., 1430 Tulane Ave., New Orleans 12, La.

Representative to Scientific Exhibit—Joseph F. Ross, M.D., 65 East Newton St., Boston 18, Mass.

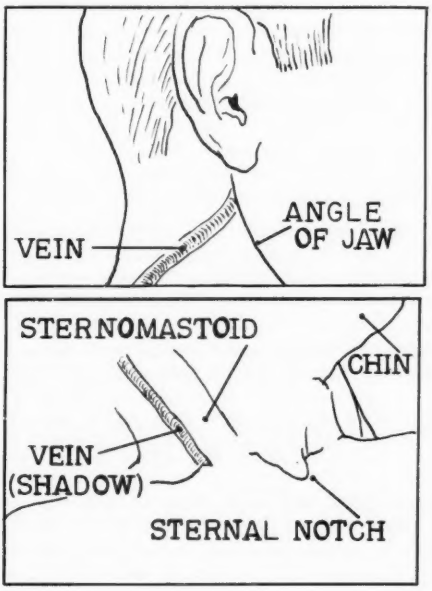
Section on General Practice

Secretary—Eugene I. Baumgartner, M.D., 25 Alder St., Oakland, Md.

Representative to Scientific Exhibit—Charles E McArthur, M.D., 1934 East Fourth Ave., Olympia, Wash.

CORRECTION

The accompanying explanatory diagrams, which were received too late to be published with the article, are to be appended to Figure 1 of "Pericardial Tamponade," by Drs. Conger Williams and Lamar Soutter (October issue, page 574).



Books

Treatment of Toxic Goiter with Radioactive Iodine. By Lindon Seed, M.D., and Theodore Field, M.S. Price, $3.75. Pp. 116, with 5 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

This book is a careful and thoughtful exposition of the problems inherent in the diagnostic and therapeutic use of radioactive isotopes, particularly I^{131}. The book will have its principal value in acquainting physicians not working actively in the field with both physical and physiological problems inherent in the use of radioactive iodine.

A general exposition of radiation physics and the physical requirements of an isotope laboratory is presented. A further section details the physiological basis of the use of radioiodine in the diagnosis and treatment of thyroid disease. The authors have carefully avoided complicating the text with extensive discussion of esoteric and controversial aspects of thyroid function. The remainder of the book is devoted to the consideration of radioiodine therapy of toxic goiter. A good discussion of proposed methods of calculating therapeutic doses is presented. The authors have evidenced a great deal of profitable scepticism concerning the calculation of dosage on the basis of fixed formulae, dependent on such factors as effective half-life of thyroidal I^{131} and estimated gland size. A discussion of therapeutic results, therapeutic indications, and hazards completes the monograph.

Interested physicians will find in this book an excellent orientation to the problems inherent in this rapidly expanding field.

Annual Review of Physiology: Volume 16, 1954. Edited by Victor E. Hall, M.D.; Frederick A. Fuhrman, M.D., and Arthur C. Giese, M.D. Price, $7.00. Pp. 545. Annual Reviews, Inc., Stanford, Calif., 1954.

The complexity of so many fields in medicine, the difficulty of reading innumerable journals in many languages, and the proliferation of specialties has increased the value of the Annual Review series, of which this volume in physiology is a worthy companion to its distinguished predecessors in the series. This is particularly true since some effort is made to view the great amorphous mass of "the literature" both selectively and critically. Since the topics change from year to year, it is a very important reference book for anyone dealing with the problems in clinical medicine or physiology included in its table of contents. The prefatory chapter, by Otto Loewi, presents an interesting departure from the usual paper, in the form of a personal essay of reflection.

Lectures on the Thyroid. By J. H. Means, M.D. Price, $3.00. Pp. 113, with 11 illustrations. Harvard University Press, Cambridge 38, Mass., 1954.

In this little book Dr. Means has incorporated five lectures given at various times and in different places but which nonetheless make a homogeneous whole. Here are embodied a medical lifetime of work and of reflections on disturbances of thyroid function, and it makes reading of the greatest interest. Dr. Means, being a little of the older school, writes against a background of the broad development of the subject, which therefore becomes alive and intelligible; nonetheless he is up to the minute in his views and indeed projects a lot of interesting questions into the future. The Harvard Press has done a fine job; there are references and an index.

Current Therapy 1954. Edited by Howard F. Conn, M.D. Price, $11.00. Pp. 898. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1954.

Current Therapy clearly fills a need in the minds of many physicians, as witnessed by the regular appearance of annual editions. It seems of special value in offering quick orientation as to the latest thing. Many doctors see only an occasional example of certain diseases such as malaria or Hodgkin's or Addison's disease. It is useful to be able to turn quickly to Current Therapy

and find the last word. On the other hand, it is not possible in such a book to give too much on rationale of treatment. Hence some of the sections take on rather a "cook book" style of prescription. This may be unwise in certain domains, such as that of the cardiac arrhythmias. On the whole, merits outweigh disadvantages: to be commended is the careful selection of real authorities, comprehensiveness, and good printing, format, indexing, etc. This reviewer would prefer to see just title and author of each section, with omission of "Method of," which conveys an impression of the possession of special tricks which is not always justified.

Leistungssteigerung, Leistungsübermüdung, Gesunderhaltung. By Dr. Max Hochrein and Doz. Dr. Irene Hochrein-Schleicher. Price, DM 27. Pp. 283. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O, 1953.

The book discusses first the psychologic factors and the influence of environment and hormonal effects upon the individual person's attitude towards work and work performance. The physiologic background of muscle exercise and of training is described in some detail. An attempt is then made to relate fatigue and exhaustion to various diseases, especially those of the circulatory system. About 100 pages are devoted to prevention of fatigue and fatigue-diseases.

Most of these preventive measures are of a poorly substantiated empirical nature. The book as a whole indulges in generalities and vagueness and adds little to factual knowledge.

Das elektrische Herzbild: Die Grundlagen eines neuen elektrokardiographischen Verfahrens. By Dr. Wilhelm Ernsthausen. Price DM 48. Pp. 231, with 227 illustrations. Hermann Rinn, Schellingstrasse 39-41, Munich 13, 1953.

The author analyzes in this book the electrical function of the heart, on the basis of the newest knowledge of electrophysiology. The metabolic function of heart muscle is reviewed. Several chapters are devoted to electrophysiological considerations. On the basis of calculation the dipole theory of the electrical field of the whole heart and single muscle fiber is rejected. Since construction of the heart vector is based on amplitudes which are modified by the electrical quality of the conducting tissue between heart and electrodes, the vector theory of the chest leads is also rejected. Instead, a new method is introduced, using two chest electrodes 3 cm. apart. Electrical fields between this bipolar electrode are measured in 1 and 0.5 cm. distances in horizontal and vertical directions and constructed in an "electrical picture of the heart." Normal and pathological heart pictures are analyzed by this method. Diffuse heart muscle changes are divided into inflammatory processes and metabolic disturbances. Difficulties of the interpretation of certain changes such as ST-T deviation in the presently used ECG methods and, especially, their quantitative relation to the state of the myocardium are well known. An attempt is made, therefore, to calculate quantitative relations by the new method, called "function diagrams" of the heart. The book describes the interpretation of the major pathological conditions by the electrical picture of the heart. However, the practical advantage of the proposed method over the presently used methods is not clearly demonstrated. Only careful clinical comparison of the two methods will decide whether the time used in the construction of the electrical picture of the heart is of enough additional value to be justified. The book is so theoretical that only those who are familiar with physics and electrophysiology will understand it. Printing, graph, and diagram material are very good.

The Atom Story: Being the Story of the Atom and the Human Race. By J. G. Feinberg, M.Sc. Price, $4.75. Pp. 243, with 30 illustrations. Philosophical Library, Inc., 15 East 40th St., New York 16, 1953.

This book is very interesting reading for one who needs a practical review of the fascinating history and development of our knowledge of the atom. The story is told in a very straightforward way but with enough scientific facts to make even a physician understand for the first time much about the atom that was unknown to him. It is surprising to find that Aristotle's influence was such a forceful detriment to the advancement of the atomic theory. However, from Democritus to E. O. Lawrence the story is a fascinating one and one which most physicians would thoroughly enjoy.

Science and Man's Behavior. By Trigant Burrow, M.D. Price, $6.00. Pp. 564, with 26 illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1953.

"Science and Man's Behavior" is really a defense and apology for the author's book "The Neurosis of Man," which is actually included in the present publication. For the casual reader, the book is a remarkable example of the predicament which the author spends so much time stressing, namely, that of man when he has lost contact with the realities of life and has thus forfeited the value which comes from criticism of one's pet ideas. Much of the book is most interesting. Many points are in agreement with current formulations and ideas about the admittedly very rough predicament man is in. In essence, the author has treated society, the world at large, as a patient and has applied modified formal psychoanalysis, which he calls "phyloanalysis," to elucidating its problems. An effort was made to break entirely with the orthodox views of medicine, history, psychiatry, and psychology. This was done under the auspices of an institute which provided a somewhat protected little world in which a small group of devoted disciples joined in an interesting experiment in mass introspection. The business of abstracting one's self from the turbulent give and take of everyday life is hazardous. The illusion of infallibility may occur, and communication may be difficult. In fact, in this instance it became so difficult that a whole new set of words had to be invented, as though there were not already more words than we can comfortably comprehend. The book leaves the impression that this strange and willful isolation was carried to an extreme in such observances as having many of the group get together for a ritual of eye closing.

My interpretation of the final conclusion which Dr. Burrow reaches is that he discovers that people are human beings. This he believes is a terrible mistake. To a novice in the field it seems most unlikely that the philosophy or the verbage invented by Dr. Burrow will do much to solve the problems of the world or of the many individuals who make it. He should be praised for the honest approach, but it contains small hope that its kind of introspection contains the key to salvation.

Hypertension and Nephritis. By Arthur M. Fishberg, M.D. Fifth edition. Price, $12.50. Pp. 986, with 49 illustrations. Lea & Febiger, 600 S. Washington Square, Philadelphia 6, 1954.

This is the fifth edition and the first revision in 15 years of this excellent reference work. The general outline of the book has remained the same. The material previously covered has been revised and brought up to date. Seven new chapters have been added. A consideration of individual processes in urine formation is now Chapter 1. Diabetic glomerulosclerosis is adequately handled in a chapter of its own. The author points out the development of the importance of chronic pyelonephritis and covers it in a new paragraph but devotes only 10 pages to it in spite of stating in the second sentence of the opening paragraph, "Indeed, if both the acute and chronic stages of pyelonephritis are included, it is doubtless much the most frequent of kidney diseases." The etiology and pathogenesis of pyelonephritis is inadequately covered in one short paragraph. The importance of pyelonephritis in the production of hypertension is well stated. However, no mention is made of pyelonephritis lenta or of the work done by Dr. George F. Dick in the production of lesions resembling "malignant nephrosclerosis" and an increased incidence of hypertension in dogs by repeated bacterial infusions without the appearance of typical pyelonephritic kidney lesions.

Another piece of new material is a discussion of the dietary management of hypertension. In particular, protein, sodium chloride, and the rice diet are discussed and their importance evaluated. Another new chapter is devoted to the newer antihypertensive drugs and includes the most recent addition, derivatives of Rauwolfia serpentina. They are completely and adequately covered in an objective fashion, and, in addition, the use of thiocyanates and their efficacy and efficiency evaluated. The present surgical approach to the treatment is also covered completely, including a consideration of total or partial adrenalectomy.

Not the least important of the new chapters is the last one, which discusses hypertension in the Cushing syndrome and pheochromocytoma.

This has always been the number one reference book on hypertension and nephritis. It still is.

Antibiotica et Chemotherapia: Volume 1. By H. Bloch, O. Gsell, and E. Langer. Price, Swiss fr. 52. Pp. 378, with 12 illustrations. S. Karger, Holbeinstrasse 22, Basle, 1954.

This handsomely printed and illustrated book is a sort of European analogue of some of the various "Advances" series which have become so popular here. There are comprehensive articles on various phases of the antibiotic problem—some in German, some in French, and some in English. The development of antibiotics, their use in endocarditis, untoward effects, secondary yeast infections, and antibiotics in pediatrics are some of the main chapter headings. There are comprehensive lists of references.

Connective Tissues: Transactions of the Fourth Conference. Feb. 18-20, 1953. Edited by Charles Ragan, M.D. Price, $3.75. Pp. 197, with 61 illustrations. Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1953.

This book is the fourth to report the proceedings of the Conference on Connective Tissues. The discussions are lengthy and, though rambling, are punctuated by careful thought, experienced judgment, and reports of original work. The conference was divided into four general topics: "General Areas of Agreement," "Isolation and Characterization of Mammalian Striated Myofibrils," "The Effect of Vitamin A on Organ Cultures of Skeletal and Other Tissue," and "An Outline of Problems to be Solved in the Study of Connective Tissues." The volume is of value to the student of connective tissue or its diseases. It is intended to stimulate thought and to further research.

Clinical Endocrinology. By Karl E. Paschkis, M.D.; Abraham E. Rakoff, M.D., and Abraham Cantarow, M.D. Price, $16.00. Pp. 830, with 253 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, 1954.

In this handsome volume the authors have presented an excellent description of clinical endocrinology. While anatomical and physiological principles are adequately discussed, the greatest emphasis is placed upon clinical features of disease—its diagnosis, manifestations, and treatment. The book is divided into twelve sections: anterior pituitary, posterior pituitary, thyroid, adrenal cortex, adrenal medulla, ovaries, placenta, testes, pancreas, parathyroids, obesity, and a section on methods and materials.

The discussions are appropriately detailed and entertaining. This is a superior text for students and practitioner alike. The simplicity of its organization makes it a source of ready reference, while its clarity and excellence of format make it a pleasure to read.

Diseases of the Liver. By Mitchell A. Spellberg, M.D., F.A.C.P. Price, $16.50. Pp. 646, with 98 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1954.

This book comprises a comprehensive account of present knowledge concerning hepatic disease. Its objective is to give the clinician a ready reference in which he can find a clear and concise account of clinical problems. This goal is achieved whether the clinician desires knowledge of the present-day status of portal cirrhosis or if his intellectual curiosity leads him to the discussion of hepatic changes in Fanconi's syndrome.

Emphasis is centered on what the author has termed the "triple spearhead" for diagnosis, namely clinical, biochemical (physiologic), and anatomic factors. The last two factors are discussed in the opening chapters, the remainder of the book being devoted to clinical conditions affecting the liver and the alterations produced in the biochemical and anatomic factors. A summary of each condition appears in bold type at the end of each subject. The bibliography is extensive and complete.

In general the book is well written, and the author makes every effort to clarify confusing subjects. In a few instances, this zeal to simplify confusing subjects overshoots the mark. A conspicuous omission is a discussion of hepatic involvement in lymphoma and related diseases.

The section on diseases of the gall bladder and bile ducts leaves much to be desired, and at times too much attention is given to rarities.

While this book is not as all-inclusive as the current two-volume edition of Lichtman, it is more readable and the summaries at the end of each chapter should be handy for practicing physicians.

The Meaning of Social Medicine. By Iago Galdston, M.D. Price, $2.75. Pp. 137. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Mass., 1954.

The average physician is much disturbed about state medicine, socialized medicine, and social medicine, and, in this country, at any rate, the predominant reaction is one of confused anguish. Galdston's book, "The Meaning of Social Medicine," should go a long way toward dispelling the confusion about differences between social and socialized medicine. He points out very clearly that social medicine encompasses the whole of present-day diagnostic and therapeutic medicine, and according to some definitions it includes preventive medicine. But, in addition, social medicine embraces hygiene and public health. As community services they function in the social units of nation, state, city, or local community. Philosophically, social medicine expresses dissatisfaction with the plight of mechanical medicine, the practice of medicine as a sort of appendage of the laboratory vaguely aware of total man but oblivious to total environment.

The development of social medicine in England, in contradistinction to socialized medicine, is set forth very clearly. What is not so clear is how may farsighted and thoughtful medical statesmen deflect the current and energies of present-day American medicine into lines which will make it of more value to society by making it more valuable to the individual. Here indeed is the urgent opportunity for coherent synthesis which will enable anyone to get a clear notion of the aims, purpose, and philosophy of social medicine. Galdston's book, while pointing to the obvious utility of such a development, does not itself supply the answers to the questions it sets forth with such clarity and insight.

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1. Freis, E.D., Finnerty, F.A., Jr., Schnaper, H.W., and Johnson, R.L.: *Circulation* 5:20, Jan. 1952.

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1. Kroop, I. G. and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95 (May) 1954.
2. Wood, H. F., and McCarty, M.: J. Clin. Investigation 30:616 (June) 1951.
3. Stollerman, G. H., et al.: Am. J. Med. 15:645 (Nov.) 1953.
4. Hedlund, P.: Acta med. Scandinav., Supplement 196:579, 1947.

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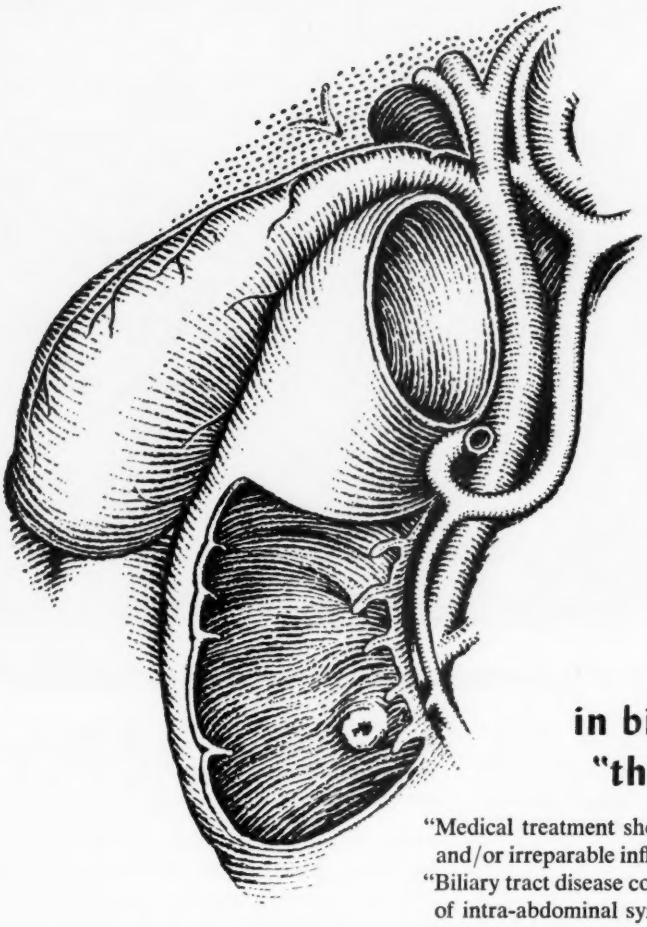

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1. Segal, H.: Postgrad. Med. *13*:81, 1953. 2. O'Brien, G. F., and Schweitzer, I. L.: M. Clin. North America *37*:155, 1953. 3. Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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1. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953.
2. Ford, R. V., and Spurr, C. L.: Am. Pract. *5*:252, 255, 256 (April) 1954.
3. Wolffe, J. B.; Walkow, M. D.; Nagler, J. H., and Anastasi, J.: J. Am. Geriatrics Soc. *2*:365 (June) 1954.

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1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

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1949 "The administration of salicylazosulfapyridine (salazopyrin) produced marked improvement in 8 of 12 cases of ulcerative colitis."
Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

1950 Bargen reports that since 1949 approximately 100 patients have been treated with Azulfidine. "The results have been extremely satisfactory in most cases."
Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.
Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.
Morrison, L. M.: Gastroenterology 21:133, 1952.

1953 Morrison publishes results from a series of 47 patients treated with Azulfidine compared to a control series of 60 patients receiving other current therapy: In the Azulfidine-series 18% are symptom-free and 52% improved, compared to 5% and 32% respectively, in the control series.
J. A. M. A.: 151:366 (Jan. 31) 1953.

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